931

IL-31 is produced by the malignant T cell population in cutaneous T-cell lymphoma and its expression correlates with pruritus

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Aim: Patients with Mycosis Fungoides and Sézary syndrome, the two most common types of Cutaneous T-cell lymphomas (CTCL), may suffer from intense pruritus, which can cause significant morbidity and decreased quality of life. IL-31, a cytokine produced primarily by CD4 T cells, has been shown to be highly associated with pruritus in atopic dermatitis, allergic contact dermatitis and prurigo nodularis. We therefore sought to investigate the relationship of IL-31 to pruritus in CTCL. Methods: PBMCs, CD4 T cells, serum and skin from CTCL patients and healthy aged matched controls were tested for presence of IL-31 mRNA or protein expression using quantitative polymerase chain reaction (qPCR), enzyme-linked immunosorbent assay (ELISA), flow cytometry, or immunohistochemistry. Results: IL-31 mRNA was increased in CTCL patient's PBMCs and CD4 T-cells, and IL-31 protein was increased in patient serum. Moreover, patients with pruritus were found to have significantly higher PBMC IL-31 mRNA ($p<0.01$) and serum IL-31 protein ($p=0.011$). Furthermore, IL-31 is primarily produced by clonal CD4 T cells in patients with a single TCR Vβ CD4+ T-cell population, and by CD4+CD26- T cells, the majority of which in each case represent the malignant T-cells. Importantly, IL-31 protein is increased in CTCL skin and co-localizes with dermal nerve fibers. Additionally, in vitro treatment using Dexamethasone, a drug that ameliorates CTCL pruritus, significantly reduced IL-31 protein expression. Conclusions: Our results suggest that IL-31 mediates itch in CTCL, and is a potential therapeutic target for anti-itch treatment.

932

Predicting treatment response in psoriasis using serum levels of adalimumab and etanercept: A single centre, cohort study

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The aim of the study was to investigate the association between serum adalimumab and etanercept levels, anti-drug antibodies and clinical response in a cohort of psoriasis patients using a commercially available enzyme-linked immunoassay (ELISA). In a single-centre cohort of 56 adults with chronic plaque psoriasis initiated on adalimumab or etanercept monotherapy between 2009 and 2011, drug and anti-drug levels were measured at the patients' routine clinic reviews (4, 12, 24 weeks of treatment and the last available observation). Responders were defined as 75% reduction in psoriasis area and severity index from baseline (PASI 75) within 6 months of treatment. Non-responders failed to achieve PASI 50 by 6 months (primary non-response) or had a loss of PASI 50 treatment response (secondary non-response). After 4 weeks of therapy, adalimumab levels were significantly higher in responders compared with non-responders ($p=0.003$) and these higher levels were sustained at 12 and 24 weeks. Anti-adalimumab antibodies were detected in 25% of non-responders (2/8 patients, average 22.5 weeks follow up) and not in any responders (n=23, average 26.1 weeks follow up). There was no significant association between etanercept levels and clinical response at 4 weeks ($p=0.317$) and no anti-etanercept antibodies were detected. In conclusion, these data are the first to demonstrate that early adalimumab drug level monitoring at 4 weeks, unlike etanercept, may be useful in predicting treatment response in psoriasis. Earlier treatment review in those with low levels may reduce drug exposure and associated cost. The prevalence of anti-drug antibodies may have been underestimated due to limitations of ELISAs and lack of trough levels. Larger studies are required to assess the clinical utility and cost effectiveness of these assays in personalising therapy in psoriasis.

933

Development of a GMP facility for cell therapy of chronic non-healing wounds

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With increasing emphasis on translational research, the need for appropriate regulatory oversight and approval has become essential. The requirements of the Food and Drug Administration (FDA) for Investigational New Drug (IND) studies that are investigators-initiated have become increasingly stringent. In this report, we focus onr developing an IND submission to the FDA and discuss the preparation and manufacturing issues facing investigators new to this type of research. At this time, the FDA is treating academic investigators (research) the same way they deal with the pharmaceutical industry. A critical obstacle is the development of Good Manufacturing Practice (GMP) facilities. GMP establishment requires the formulation of Standard Operating Procedures (SOPs) for each piece of equipment, procedures, quality assurance, personnel training, and documentation. Presently, our Institution has 3 GMP facilities. There is a strong relationship between the GMP, the clinical research team, the Institutional Review Board (IRB), and FDA regulations. For the purpose of overcoming these challenges, we will take the example of culturing autologous bone marrow-derived mesenchymal stem cells (MSCs), expanded in culture, for topical application to non-healing human wounds. In this work, we have shown that MSCs delivered at a concentration of greater than 1.5 million per cm2 of wound surface lead to accelerated healing of previously non-healing wounds. We developed a stem cell delivery system by using a modified fibrin spray construct. All components of this proof of principle treatment, including cells, media, and fibrin are subject to SOPs and regulatory issues. The development of the GMP facility for this work and the subsequent IND submission to the FDA are a formidable task which academic investigators are not yet familiar with.

934

***In vitro* cytokine expression by PBMCs in the diagnosis of herbal drug-induced skin eruption**

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Herbal medicine is now widely used throughout the world, and administration of herbal drugs has been reported to be associated with several potential side effects such as skin eruptions. Herbal drugs are produced by combining multiple crude drugs, mostly of plant origin. Therefore, determining precisely what kind of medicinal plants are associated with the herbal drugs that induce skin eruptions is often difficult. This study investigated the expression of several cytokines mRNA in peripheral mononuclear cells (PBMCs) from patients with herbal drug-induced skin eruptions in order to establish effective methods for diagnosing the cause of such skin eruptions. Two patients with drug reaction were examined; one patient developed skin eruptions due to keishibukuryogan (KBG), which is composed of 5 medicinal plants, Cinnamomi cortex, Paeoniae Radix, Moutan cortex, Persicae semen and Hoelen, and the other patient reacted to senna. PBMCs from the two patients were cultured with the supernatant from the medicinal plants from KBG or senna in various concentrations for 24 h and an RT-PCR analysis was performed. The results showed a high mRNA level of interleukin (IL)-4 and IL-5 to be detected in PBMCs stimulated by KBG, Cinnamomi cortex and Moutan cortex from the KBG-induced drug patient. Senna stimulated a high level of IL-4 and IL-5 mRNA levels in PBMCs from patient with senna-induced drug reaction. On the other hand, PBMCs from the normal subjects exhibited no such stimulation. These finding indicate that the measurement of medicinal plants-induced IL-4 and IL-5 mRNA in PBMCs may therefore be a useful in vitro diagnostic tool for identifying the cause of herbal drug-induced skin eruptions.

935

12 weeks of treatment with an oral SIRT1 activator, SRT2104, leads to clinical improvement and skin microarray modification in patients with psoriasis

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Activation of the NAD+-dependent deacetylase, SIRT1, is an unexplored therapeutic approach for treatment of inflammatory diseases.Forty patients were randomized 4:1 to three escalating doses of SRT2104 (250, 500, 1000 mg PO qd) or placebo.Across all SRT2104 groups, 34.6% of patients (9 out of 26; 90% CI 18.0%-54.2%, $p<0.0001$) with pre- and post-treatment biopsies achieved good to excellent histological improvement.We conducted microarray analysis in skin biopsies from a subset of subjects which included subjects with good to excellent histological improvement (responders) and those which did not achieve histological improvement (non responders).We observed that SRT2104 treatment modulated gene expression of psoriatic gene phenotype believed to be central to the psoriasis pathogenesis including IFNγ, TNFα, IL-17 signaling and keratinocyte differentiation.A total of 27 subjects (69%) across all treatment groups, including placebo, experienced at least one treatment emergent adverse event.The majority of AEs were either mild or moderate.The most common AEs were headache (8%), dizziness (8%), upper respiratory tract infection (8%), and psoriatic arthropathy (8%). Average drug exposure increased in a dose-dependent manner for escalating doses of SRT2104. Between-patient variability in exposure was high (AUC CV: 51-89%). In summary, SRT2104 demonstrated signs of clinical activity, suggesting that modulation of psoriasis through SIRT1-mediated pathways may represent a novel approach to the management of this disease. Further study is warranted.

936

Allogeneic fibroblast cell therapy accelerates wound healing in recessive dystrophic epidermolysis bullosa (RDEB)

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Fibroblast cell therapy can modify disease biology in RDEB although its impact on wound healing is not clear. We compared allogeneic fibroblasts (ICX-RHY-013; sterile suspension of 20x106 per ml of allogeneic human dermal fibroblasts in Hypothermosol®-FRS vehicle) injected intradermally into erosion margins of individuals with RDEB, with injections of vehicle only, to assess safety and efficacy. We enrolled adult RDEB subjects with chronic erosions in a phase II, double-blind, randomised, vehicle-controlled trial. Erosions were randomised in a computer-generated block 1:1 ratio, to either a single treatment of 5x106 fibroblasts per linear cm of erosion margin or to a similar volume per linear cm of erosion margin of vehicle. All subjects continued standard wound care. The trial sponsor, statistician, participants and the investigator conducting the study assessments and follow up visits were masked to treatment allocation. The main endpoint was mean area change in treated erosions at the end of 6 months. Analyses were by intention to treat. 26 erosions in 11 RDEB subjects were injected; 14 erosions received ICX-RHY-013 and 12 vehicle alone. All follow-up visits were completed for each case. Percentage erosion area decreased rapidly after active treatment. Treatment difference between ICX-RHY-013 and vehicle was -23.5% (CI -3.5 to-43.5, $p=0.025$) at day 7, -19.15% (CI 3.36 to -41.66, $p=0.089$) at day 14 and -28.83% (CI 7.97 to -65.63, $p=0.11$) at day 28. Beyond day 28, however, changes in mean erosion area did not differ significantly between the two groups, although blinded independent assessment of photographs showed that 78.6% and 92.8% of the erosions treated with ICX-RHY-013 were clinically better from baseline at 28 days and 6 months, respectively. Intradermal injections of allogeneic fibroblasts increase the rate of erosion healing in subjects with RDEB within the first 28 days although further studies will be needed to address optimal cell dosage and frequency of re-treatment.

937

Multiple congenital melanocytic naevi and neurocutaneous melanosis are caused by post-zygotic activating mutations in codon 61 of *NRAS*, increasing the risk of melanoma in affected tissues

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Multiple congenital melanocytic naevi (CMN) can be associated with a range of neurological abnormalities, and an increased risk of melanoma in both skin and CNS. Mutations in NRAS, BRAF and Tp53 have been described in individual CMN samples, however, their role in the aetiology of multiple CMN in a single individual has not been studied. We hypothesised that a single post-zygotic mutation in NRAS could be responsible for multiple CMN in the same individual, as well as for melanocytic and non-melanocytic central nervous system (CNS) lesions. Fifty-five samples from 15 patients with multiple CMN were sequenced after site-directed mutagenesis and enzymatic digestion of the wild-type allele. Oncogenic missense mutations in codon 61 of NRAS were found in affected neurological and cutaneous tissues of 12/15 patients, but absent from unaffected tissues and blood, consistent with NRAS mutation mosaicism. In ten patients the mutation was consistently c.181C>A, p.Q61K, and in two c.182A>G, p.Q61R. All 11 non-melanocytic and melanocytic CNS samples from five patients were mutation positive, despite NRAS rarely reported as mutated in CNS tumours. Transition from heterozygosity to homozygosity was associated with the onset of melanoma, implying a multi-step progression to malignancy. These results suggest that single post-zygotic NRAS mutations are responsible for multiple CMN and the associated neurological lesions.

938

Raised serum levels of complements in patients with cutaneous polyarteritis nodosa

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Cutaneous polyarteritis nodosa (CPN) is a necrotizing vasculitis of medium-sized arteries within the skin, without the involvement of internal organs. Increasing evidence of complement activation in the pathogenesis of systemic vasculitis has been reported in recent studies. We measured serum complement 3 (C3), C4, total complement hemolytic activity (CH50), and creatinine in 101 patients with CPN to determine the correlations among clinical parameters. We retrospectively investigated 101 patients with CPN seen at our university between 2003 and 2012. We measured levels of serum C3, C4, and CH50 with a commercial immunoassay. We found that the prevalence of inflammatory plaques, arthralgia, and myalgia was significantly higher in patients with mononeuritis multiplex than in the other patients. Serum creatinine titers of patients with mononeuritis multiplex were significantly higher than those in the other patients. We found significantly positive correlations between CRP and CH50 titers in serum among all CPN patients ($p<0.001$). A similar significant trend was seen in C3 and C4 titers among the CPN patients ($p<0.001$). Positive significant correlations were also observed for CRP and serum creatinine levels in these patients ($p<0.001$). In conclusion, we suggested that complement activation participated in the development of CPN. We further speculated that mononeuritis multiplexes present a risk factor for developing renal insufficiency.

939

Targeted sun exposure guidance for South Asians living at northerly latitude could assist avoidance of vitamin D deficient status (25[OH]D <10 ng/mL)

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Low vitamin D status remains prevalent in S.Asians living at northerly latitudes despite dietary advice. It is known that following general recommendations on summer-sunlight exposure (geared for white skinned people) has little impact on their vitamin D status. As their skin cancer risk is low, increased sun-exposure may be appropriate to assist their status. We thus examined the efficacy of a dose-range of simulated UK summer sunlight exposures in raising vitamin D status in adults of S.Asian ethnicity. Healthy S.Asians (n=60, 20-60y) received one of 6 UVR exposures ranging from 0.65-3.9 SED, equivalent to 15-90 minutes midday summer-sunlight at 53.5°N (Manchester, UK), 3x/week for 6 weeks. This occurred in a whole body cabinet (95% 320-400 nm, 5% 290-320 nm), while wearing casual clothes to reveal 35% skin area. Serum 25-hydroxyvitamin D (25[OH]D) was measured weekly. Mean dietary vitamin D intake was 2 µg/day (range 0.12-14.48). At baseline, all completing participants (n=51) were vitamin D insufficient (25[OH]D <20 ng/mL) with 90% deficient (<10 ng/mL, a level associated with osteomalacia and rickets). Post-course, only 6/51 attained 20 ng/mL 25(OH)D. Level of 25(OH)D increased in all groups ($P\leq0.01$). Rise in 25(OH)D increased with UVR dose to 3.25 SED, this group had a mean±SD rise of 12.7±7.8 ng/mL ($P<0.01$) and attained 18.0±6.2 ng/mL post-course. Notably, the majority (94%) of those volunteers receiving exposure doses ≥1.95 SED achieved 25(OH)D >10 ng/mL (n=31, mean±SD 15.7±5.0 ng/mL), equivalent to ≥45 minutes unshaded midday sunlight exposure at UK latitude. Targeted sunlight exposure guidance to S.Asians could enhance vitamin D status to a level to avoid deficiency. However, more effective advice on oral vitamin D intake is required for S.Asians living at northerly latitude to achieve 25(OH)D ≥20 ng/mL.

940

Adalimumab effects on C-reactive protein and sleep in patients with moderate to severe psoriasis and suboptimal response to etanercept, methotrexate, or phototherapy: Subanalysis of the PROGRESS study

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Introduction: To evaluate the effects of adalimumab (ADA) on high sensitivity C-reactive protein (hsCRP) levels and sleep in psoriasis patients (pts) with suboptimal response to other treatments. Methods: Data were analyzed from a 16-week (wk) open-label trial (PROGRESS; NCT00566722) that enrolled pts with moderate to severe psoriasis and suboptimal response to ETN, MTX, or NB-UVB. Pts discontinued therapy 2 wks (ETN) or 1 wk (MTX, NB-UVB) before initiating ADA (80mg wk 0; 40mg every other wk). Primary endpoint: proportion of pts achieving PGA of clear or minimal at Wk 16. Changes from baseline to Wk 16 in hsCRP concentration and in Medical Outcomes Study Sleep Scale Sleep Problems Index II (SPI-II; 0-100 scale; higher scores indicate more sleep problems) were evaluated. Regression analyses for the overall pt group determined correlations between hsCRP and SPI-II at baseline and Wk 16. Results: 152 pts enrolled (ETN, N=82; MTX, N=41; NB-UVB, N=29). At baseline, 1.3% and 0% of all pts had PGA scores of minimal or clear, respectively. At Wk 16, 52.0% of all pts reached PGA of clear or minimal. Baseline mean hsCRP concentrations were 5.0mg/L for all pts (n=142). Median hsCRP change from baseline to Wk 16 for all pts was -0.30mg/L (n=119); for pts who discontinued ETN, -0.35 (n=64); MTX, -0.30 (n=33); NB-UBV -0.20 (n=22). At baseline, hsCRP values were not associated with SPI-II values after adjusting for baseline BMI ($P=0.565$). At Wk 16, change in hsCRP from baseline was statistically significantly correlated with change in SPI-II from baseline after adjusting for baseline SPI-II, hsCRP and BMI ($P=0.006$). Conclusions: ADA treatment in moderate to severe psoriasis pts with suboptimal response to ETN, MTX, or NB-UVB resulted in hsCRP reductions associated with improved clinical response and sleep.

941

Non-invasive diagnosis of basal cell carcinoma subtype by reflectance confocal microscopy

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In vivo reflectance confocal microscopy (RCM) is a non-invasive imaging technique, which is able to image the skin at a cellular resolution. Currently, RCM is used for diagnosis of melanoma and non melanoma skin cancer including basal cell carcinoma (BCC). Until now, it is not possible to distinguish between subtypes of BCC using RCM. Therefore the purpose of this study was to establish RCM features for the nodular, micronodular and superficial subtype of BCC. In 14 patients, 27 suspicious lesions for BCC were selected for RCM imaging. For histological evaluation, a 3-mm punch biopsy was obtained and stained with hematoxylin-eosin. In total, 13 biopsy proven BCCs were found. It was demonstrated that tumor nests, peripheral palisading, branch-like structures, fibrotic septa and increase of vascular diameter were characteristic RCM features for nBCC and mnBCC. Size and shape of the tumor nests allows further distinction between nBCC and mnBCC. Solar elastosis and the location of the tumor nest just below or in connection with the basal cell layer characterizes sBCC. This study presents novel RCM features for BCC, which allow in vivo diagnosis of the nodular, micronodular and superficial subtype of BCC. Additionally, the complete lesion can be evaluated non-invasively.

942

Clindamycin 1%/benzoyl peroxide 3% gel, a new topical combination product, is effective in Japanese patients with acne vulgaris

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A randomized, multicenter, single-blind, active-controlled trial was conducted to demonstrate the superiority of clindamycin1% (CLDM)/benzoyl peroxide (BPO) 3% twice daily (BID) to CLDM-BID, and the non-inferiority of CLDM/BPO3% once daily (QD) to CLDM-BID, using acne total lesion (TL) counts. Main inclusion criteria were 12-45 years of age, with an Investigator Static Global Assessment (ISGA) score ≥2 (mild), 17-60 inflammatory lesions (IL) and 20-150 non-IL. A total of 800 Japanese patients were randomized (2:3:3) to receive CLDM/BPO3%-QD, CLDM/BPO3%-BID, or CLDM-BID for 12 weeks. Efficacy was based on absolute and percent reductions in TL, IL, and non-IL counts, and improvement in ISGA. Safety variables were adverse events (AEs), laboratory tests, vital signs and local tolerability. Adjusted mean change in TL counts from baseline to Week 12 in CLDM/BPO3%-BID was superior to CLDM-BID: difference -11.1 (95%CI; -15.3, -7.3); $p<0.001$ (ITT population). Adjusted mean change in TL counts from baseline to Week 12 in CLDM/BPO3%-QD was non-inferior to CLDM-BID: difference -8.4 (95%CI; -13.2, -3.6); $p<0.001$ (per-protocol population). Mean absolute and percent reductions in TL, IL, and non-IL counts at Weeks 1, 2, 4, 8 and 12 were greater in CLDM/BPO3%-QD/-BID than in CLDM-BID. The percent of patients with at least a 2-grade improvement in ISGA from baseline to Week 12, and who had an ISGA of 0 or 1 (clear or almost clear) at Week 12 were significantly higher in CLDM/BPO3%-QD/-BID than in CLDM-BID ($p<0.001$). CLDM/BPO3%-QD/-BID were well tolerated, with AEs that were mostly mild-to-moderate, and no clinically relevant changes in laboratory tests or vital signs. Mean changes in erythema, peeling and itching scores were similar in all 3 groups. Dryness and burning/stinging scores at Weeks 1 to 4 were slightly higher in CLDM/BPO3%-QD/-BID than in CLDM-BID. CLDM/BPO3% QD or BID for 12 weeks was more effective than CLDM alone in the treatment of Japanese patients with acne vulgaris, and was safe and well-tolerated.

943

Medication adherence, healthcare costs and utilization associated with acne drugs in the United States

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The objective of this study was to examine medication adherence, healthcare costs and utilization associated with acne drugs among acne patients in the United States. This was a retrospective cohort study from January 2004 to December 2007 using the Marketscan Medicaid Database, a US national healthcare claims database. Acne patients aged 0-64 years were followed for 90 days after their first acne related drugs were prescribed to measure acne medication adherence, acne related outpatient visits, and total acne related healthcare costs. Adherence was measured among different acne related drug classes using Medication Possession Ratio (MPR). Multivariate regression analyses were conducted to assess the outcomes. A total of 24,438 eligible patients were included, and 89.39% were aged less than 18 years. The average adherence to acne drugs (MPR) was 0.34, and only 11.74% of the patients were considered as adherent (MPR≥0.80). Patients with drug refills had higher adherence rate (MPR=0.74) than who those without refills (MPR=0.27). Factors significantly associated with adherence were age, comorbidity, gender, and number of drug refills. Patients were more adherent to oral retinoids than any other acne drug classes (MPR=0.78, 57% considered as adherent). Adherence to oral antibiotics (MPR=0.21) and topical agents in acne patients was quite poor. After controlling for medication use behavior, using oral antibiotics decreased the number of acne related outpatient visits by 51.3% ($p<0.001$) and lowered the acne related total costs by 51.6% ($p<0.001$). Topical agents generally had better utilization and cost outcomes compared to oral drugs. Developing strategies to improve adherence to drugs with relatively favorable utilization and cost outcomes such as topical agents and oral antibiotics among teenage acne patients is warranted.

944

Palliative treatment for in-transit cutaneous metastases of Merkel cell carcinoma using surface-mold computer-optimized high-dose-rate brachytherapy

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Merkel cell carcinoma (MCC) is a rare and often fatal cutaneous neuroendocrine carcinoma. Despite aggressive management with wide local excision and radiation therapy, locoregional recurrence and metastatic progression are common. Treatment of in-transit cutaneous metastases is challenging as they are often multifocal, tend to be located on the curved surfaces of the extremities making conventional external beam radiation therapy technically challenging. In-transit lesions are often too numerous for clear margin excision, and resection carries risks of poor wound healing in the setting of evolving lymphedema. Surface-mold computer-optimized high-dose-rate brachytherapy (SMBT), a novel form of radiation therapy, overcomes these limitations and offers a well-tolerated palliative treatment for local control. A retrospective study of ten patients with in-transit cutaneous MCC metastases treated with SMBT at the Dana-Farber/Brigham & Women's Cancer Center between 2006 and 2012 was done. Eight patients had in-transit metastases on the extremities (80%) and 2 on the head & neck (20%). All 152 metastatic MCC lesions treated with SMBT resolved clinically within a few weeks of therapy with minimal side effects. The median follow-up was 34 months (range 22-85 months). Two of 152 treated lesions recurred for a local control rate of 99%. Eight patients (80%) developed additional in-transit metastases outside the original SMBT fields. Five of these 8 patients underwent additional SMBT. At study conclusion, three patients (30%) are alive without disease, 3 patients (30%) are alive with disease, and 4 patients (40%) died of MCC. SMBT offers a novel, effective and durable palliation for cutaneous MCC metastases.

945

A novel interleukin (IL)-8 reporter cell line, THP-G8, can evaluate anti-tumor necrosis factor (TNF)-α neutralizing activity of patients' sera and predict drug effectiveness during anti-TNF-α antibody therapy

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Anti-TNF-α antibodies (ATA) have become an essential component of psoriasis therapy. However, secondary loss of drug effectiveness in patients receiving ATA is a common problem. Although the presence of antibodies against ATA (anti-ATA Abs) has been shown to reduce the clinical response to the drug, it is not easy to accurately measure the serum level of anti-ATA Abs because residual ATA can mask the presence of anti-ATA Abs. Recently, we have established an IL-8 reporter cell line, THP-G8, which is derived from a human monocyte cell line, that harbors SLO and SLR luciferase genes under the control of IL-8 and G3PDH promoters, respectively. This stable cell line responds to TNF-α by augmenting SLO luciferase activity (SLO-LA) in a dose-dependent manner. In addition, pretreatment of TNF-α with ATA, such as with infliximab, adalimumab, or golimumab, suppressed SLO-LA dose-dependently. Accordingly, we examined whether THP-G8 could enable us to detect anti-TNF-α neutralizing activity in the sera of psoriasis patients during ATA therapy. We cultured THP-G8 for 6 h in the presence of 10 ng/ml of human recombinant TNF-α with or without serially diluted patients' or healthy controls' sera. The sera of healthy controls or psoriatic patients who were not treated with ATA (n=2) did not affect the TNF-α induced SLO-LA. On the other hand, the sera of 4 patients who were treated 1 to 4 weeks before and achieved more than PASI 75 showed significantly inhibited TNF-α induced SLO-LA ($p<.0001$, EC50 value=1/8-3/8 dilution of serum). In contrast, the sera of 3 patients treated two weeks before who were resistant to ATA did not show inhibition of TNF-α induced SLO-LA. These data suggest that this cell line provides a useful tool to evaluate anti-TNF-α neutralizing activity of patients' sera that correlates with the effectiveness of ATA in each patient.

946

An instrument-applied topical product affects skin microvasculature and may therefore be beneficial for improving the appearance of cellulite

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Cellulite is a result of fat deposits often occurring on the hips, buttocks and thighs creating a dimpling, orange-peel appearance on skin. Vasoconstriction often accompanies the formation of cellulite but it is not known whether this results from the increasing adipocyte size or is causative. Nevertheless, vasoconstriction results in reduced blood flow reducing nutrient supply to upper areas of the skin, weakening the skin's connective tissues and possibly contributing to the dimpling effect seen in persons with cellulite. Ten Caucasian female subjects, Fitzpatrick type I and II, age 20 – 35, BMI 20-30 were enrolled in a pilot study to assess the ability of two electrically-conductive topical products, used in conjunction with a cosmetic instrument delivering a mild pulsating electrical current, to improve microcirculation. Each of two topical products was applied to the dorsal surface of the upper legs, one on each leg of each subject, and very gently massaged into the skin for 5 minutes using a microcurrent-delivering instrument. Immediately following the treatment fluid movement was measured by laser Doppler, infrared imaging and chromameter. Over baseline, by laser Doppler measurement, a statistically-significant increase in fluid movement was seen with both instrument-applied topical gels. Chromameter data showed non-statistically significant but directional increases in fluid flow. Infrared imaging showed a significant cooling effect on the skin from both instrument-applied gels suggesting that fluid movement was not the result of thermally-induced vasodilation. Microcurrent-delivered cellulite topical products may exhibit enhanced efficacy due to increases in microvascular circulation.

947

Debio 0932, a new oral HSP90 inhibitor, prevents inflammatory cytokine release and alleviates psoriasis in a xenograft transplantation model

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Debio 0932 (D0932) is a new oral heat shock protein 90 (HSP90) inhibitor being tested clinically as anti-cancer therapy. In a Phase I study in patients with solid tumors, a subject with a 20-year history of psoriasis, reported complete disappearance of hyperkeratosis upon D0932 treatment (800 mg QD). HSP90 is a highly abundant intracellular chaperone involved in folding, stability, and activity of many client proteins including growth factor receptors and signaling kinases. Inhibition of HSP90 results in an increased degradation of misfolded oncoproteins and leads to tumor growth inhibition. HSP90 may play a role in psoriasis as key signaling kinases involved in inflammation (e.g. JAK/STAT, ERK1/2) are clients of HSP90 and anti-inflammatory effects of HSP90 inhibitors have been observed *in vivo*. The objective of the present study was to evaluate the ability of D0932 to alleviate psoriasis in preclinical models. *In vitro*, D0932 was shown to fully block the release of IFNγ, TNFα, and IL17 in activated primary T-cells, at concentrations above 100 nM, without affecting cell viability. D0932 also inhibited inflammatory cytokine secretion and cell proliferation in monocyte and keratinocyte cell lines. *In vivo*, the ability of D0932 to treat psoriasis was evaluated using immune-deficient mice xenografted with involved psoriatic skin from 5 psoriasis patients. Xenografted mice were treated orally, with 80 mg/kg D0932 QD for 3 weeks. D0932 treatment significantly decreased both the semi-quantitative clinical psoriasis score and the epidermal thickness measured on HE stained biopsy sections from the treated grafts compared to vehicle treatment. In conclusion, D0932 demonstrated anti-inflammatory and anti-proliferative activities *in vitro*, and efficacy in mice bearing xenografted psoriasis skin, *in vivo*. These data suggest a strong therapeutic potential of D0932 for the treatment of psoriasis.

948

Hyperuricaemia in patients with chronic plaque psoriasis

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Background Hyperuricaemia is a well-known metabolic risk factor for cardiovascular diseases. Chronic plaque psoriasis is frequently associated to metabolic co- morbidities and cardiovascular diseases. Objective To measure serum uric acid in patients with chronic plaque psoriasis. Methods Serum levels of serum uric acid in 119 patients with psoriasis and 119 controls matched by age, sex and body mass index (BMI). Results Psoriatic patients had serum uric acid levels higher than controls (5.6 +/- 1.6 mg/dL vs 4.87 +/- 1.4mg/dL; $p<0.001$). In the multivariate logistic regression analysis psoriasis was associated to hyperuricaemia independently of age, sex, BMI, presence of diabetes and hypertension. Conclusions Patients with psoriasis may have a tendency to hyperuricaemia which predispose to higher cardiovascular risk. Dietary and/or pharmacological correction of hyperuricaemia appear relevant to the global management of patients with moderate to severe psoriasis.

949

Topical diphencyprone (DPCP) induces distinct early and late cellular immune reactions in human skin

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DPCP is a hapten that can induce T cell recall or delayed-type hypersensitivity (DTH) reactions in human skin and is used as a treatment for cutaneous melanoma metastases. To characterize tissue reactions to DPCP, we sensitized and then studied recall responses in 11 healthy subjects (open label design). The recall DTH reactions, as well as placebo-treated sites, were biopsied at 3 days (classic DTH peak response) and 14 days after challenge. Biopsies were bisected for cellular phenotyping by immunohistochemistry and measurement of gene expression. Clinically, DTH responses were strong at day 3 in all 11 individuals but decreased at day 14. Day 3 reactions were characterized by marked CD3+ T cell and CD11c+ dendritic cell (DC) infiltrates, with strong upregulation of IL2, IFNG, CD25, granzyme, and granulysin mRNAs (>7,500 genes had statistically significant changes as measured by gene arrays). A surprising finding was seen in day 14 biopsies, as T cell and DC infiltrates persisted, DC maturation (DC-LAMP+ cells) increased, and 5 of 11 subjects had increased cellular infiltrates compared to day 3 reactions. To assess the balance of activation/inflammation-associated vs. regulatory molecules in DTH reactions, gene array and RT-PCR measures were compared at day 3 and day 14. In general, negative immune regulators such as IDO1, CTLA4, and Foxp3 were highly upregulated in day 3 reactions and strong expression persisted into day 14 reactions, while T cell cytokines such as IL2 and IFNG had peak responses at day 3. Subjects who had decreased immune infiltrates at day 14 had higher expression of regulatory genes at day 3. Our data suggest two phases of a DTH response: 1) early infiltration/inflammation (classic DTH response) and 2) prolonged resolution phase (resolving inflammation) for 2-3 weeks with a distinct pattern of gene expression. Eventually, all subjects had complete resolution of infiltrates after 4-8 months. These data provide key insights into negative regulation of cutaneous immunity in a DTH reaction.

950

Human cathelicidin (hCAP18/LL37) in pustules contributes to the pathogenesis of palmoplantar pustulosis

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Palmoplantar pustulosis (PPP) is a chronic recurrent dermatosis characterized by intraepidermal vesicles filled with neutrophils. We reported that the vesicles of PPP before pustule formation originated from eccrine sweat glands in the acrosyringium (JID 2010), and that the granules of polymorphonuclear leukocytes (PMNs) contained human cathelicidin (hCAP18/LL37). Given the formation of pustules in the skin, we hypothesized that a malfunction in cathelicidin processing by the PMNs in pustules contributes to the pathophysiology of PPP, because abnormal enzymatic processing of cathelicidin by the proteinase KLK-5 or KLK-7 in rosacea results in skin inflammation (Nat Med 2007). [Methods] PMNs were collected from the pustules and peripheral blood of PPP patients for ELISA and Western blotting (WB). A skin biopsy from PPP lesional skin was performed for immunostaining. A living skin equivalent (LSE) system was established, and we checked whether exogenous cathelicidin through the skin barrier could induce inflammatory cytokines, as in PPP lesional skin. [Results] Cathelicidin expression was detected in the eccrine glands of the dermis, the stratum corneum (SC), and sweat ducts in the SC, but not in epidermal keratinocytes (KCs) in control skin. PMNs in the upper area of the PPP pustules showed cathelicidin expression in the granules, even though the epidermal KCs showed no over-expression. However, WB for cathelicidin in PMNs from PPP peripheral blood and pustules showed high levels of the active form (4.5 kDa) compared with PMNs from control peripheral blood. Exogenous cathelicidin (10 μM) through the skin barrier upregulated IL-17C and IL-8 mRNA levels in the LSE. This suggests that PMN cathelicidin (LL37) contributes to secondary inflammatory phenomena in lesional skin after pustule formation in PPP

951

The prevalence of obesity is increased in patients with late compared to early onset psoriasis after adjustment for age

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The objectives of our study were to compare the clinical and epidemiological characteristics of early and late onset psoriasis with an emphasis on potential differences in the comorbidities associated with each subtype. Our observational, multicentre study was performed between 2010 and 2011 with the cooperation of 32 Hungarian dermatologists who collected data from 377 psoriatic patients at outpatient clinics. Associations between the age at the time of diagnosis and binary comorbidity outcomes were evaluated using multiple logistic regression analysis adjusted for age and other relevant confounders. No significant differences were observed in disease severity between the two subgroups. Obesity and increased abdominal circumference were more prevalent in subjects with late onset psoriasis than in those with early onset psoriasis. An increased prevalence of positive family history, scalp involvement as an initial symptom, psoriatic arthritis and depression was observed in patients with early onset psoriasis. These results may support the hypothesis that the manifestation of psoriasis is influenced primarily by genetic factors in individuals with early onset psoriasis and by metabolic factors, especially obesity in patients with late onset psoriasis. The observed differences in the traditional and metabolic comorbidities associated with early and late onset psoriasis support the usefulness of these subclassifications for routine clinical practice.

952

Pilot double blind multi-centre randomised controlled trial of hand held NB-UVB home phototherapy for focal or early vitiligo

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Hand held NB-UVB units are portable and light weight devices. Currently in the UK, phototherapy is usually reserved for widespread vitiligo and requires frequent hospital visits. Some evidence exists that treating vitiligo early may enhance the chance of successful repigmentation. Early treatment of limited vitiligo may be a promising approach. This pilot trial determined the feasibility of conducting a large multi-centre RCT involving hand held home phototherapy. The primary objective was to establish the proportion of eligible participants and their willingness to be randomised. Secondary objectives included preparing an educational package on how to use the intervention, to deal with possible side effects, establishing participants adherence to the treatment and testing the primary outcomes for the main trial (repigmentation, quality of life, cessation of spread). This was a 3 arm placebo-controlled parallel trial. 2 devices were tested: Group A-active Dermfix; Group B-active Waldmann; Group C-placebo Dermfix. 29 participants were randomised and treated for 4 months with NB-UVB at home. Patients received training on baseline visit. Outcomes were assessed on baseline and after 16 weeks of treatment. Patients and investigators were blinded. Recruitment was completed in 3 instead of anticipated 6 months. Response rate for primary care and secondary care was 40% and 79% respectively. We identified 54/97 (55.6%) eligible patients but were able to allocate only 29 due to limited resources available. 90% (25/29) of patients adhered with the treatment. 11 of 17 (65%) in active groups had some degree of repigmentation, especially on face and neck. Both devices have similar characteristics including output pre and post-trial and acceptability to participants. The pilot trial showed that vitiligo patients are keen in participating in trials on home light therapy. The educational package was comprehensive and suitable for implementation at home.

953

Vascular inflammation and innate immunity modulation: Ways for skin blemishes correction

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Numerous factors such as modern-life associated stress, chemical or mechanical aggressions, UV radiations can lead to the development of cutaneous blemishes (redness, pimples, spots…). At the cellular and molecular level these imperfections are first initiated by an inflammatory reaction that can involve aspecific, vascular or neurogenic mediators. A new active ingredient, schizandra hydrolysate (SH), for skin blemishes correction, was evaluated in vitro and in vivo. In normal human epidermal keratinocytes (NHEK), SH significantly inhibited the pro-angiogenic factor VEGF at the protein level (measured by ELISA) in response to PMA (-72%, $p<0.001$) and at the gene level (-89%, $p<0.001$) (measured by real-time RT-PCR). Moreover, SH reduced FGF2 (-93%, $p<0.001$) and stimulated thrombospondin-1 (+118%, $p<0.01$) gene expressions. SH significantly modulated VEGF-induced proliferation of human dermal microvascular endothelial cells (-52%, $p<0.05$) as assessed by intracellular phosphatase activity. SH significantly reduced KLK5 (-54%, $p<0.01$) and LL37 (-58%, $p<0.01$) gene expressions in calcitriol-treated NHEK, demonstrating its ability to normalize innate immunity. A double-blind, placebo controlled trial was performed on 60 volunteers with installed redness. A cream with 0.5% SH was applied twice daily on the whole face for 56 days. Efficacy on redness was evaluated by cross polarized digital images analysis and self-assessment questionnaires at D28 and D56. SH significantly reduced facial redness especially on blood vessels area criteria (-44.6%, $p<0.05$) and on the contrast between redness and healthy skin (-41.2%, $p<0.05$). SH regulates the main pathways of vascular inflammation via a modulation of angiogenesis and vasodilation and, moreover, shows a normalizing effect of innate immunity. These in vitro activities are translated in the clinical improvement of facial redness and contrast resulting in a corrective and unifying effect on complexion.

954

After daily application for two weeks, continued presence of naftifine is seen in the stratum corneum up to four weeks following the last application

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Two-week treatment using naftifine cream 2% has been shown to be efficacious in subjects with Tinea pedis and cruris, and in most cases, continued improvement has been observed following cessation of treatment for up to four weeks. One possible explanation for continuous post-treatment improvement is drug-levels remaining in the stratum corneum (SC). Drug-levels in the SC are often measured using tape stripping methodology, which enables the selective removal of the SC layers in order to be able to assess the presence and amount of drug in the skin. We hypothesize that drug-levels of naftifine that may be of clinical relevance will be found in the SC four weeks after last application. This was an open-label, single-exposure study on subjects comparing the amount of drug that was absorbed into the SC following application for 2-weeks. Twelve subjects were dosed daily (6 with naftifine cream 2% and 6 with naftifine gel 2%). Enrolled subjects had a total of twelve 8cm-squared test application sites demarcated on the back. A total of 25 individual sequential strips were obtained from each test site. Of these, a total of 11 sites were dosed once daily with the drug (5.0μL/cm-squared) for days 1 to 14 and the final site remained untreated to serve as the control site. On days 15, 29, and 43, a selected test site was stripped to collect the SC in order to process the amount of drug present over 28 days following the last dose. Naftifine was present on all tape strip samples collected over the 28 days period following two weeks of application. The most relevant, deeper tape strip sets reflecting the SC, showed potentially clinically relevant presence of naftifine in the skin for 28-days post-treatment. Naftifine was present in the tape strips on all sample collection days up to four weeks following the last drug application. These findings help explain the progressive improvement in clinical and mycological response rates during the treatment period and for up to four week post-treatment in the clinical trials using naftifine.

955

Both ketoprofen in transfersome (IDEA-070) and drug-free vehicle (TDT 070) improved symptoms in patients with inflammatory skin diseases

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There is preliminary evidence that ketoprofen in ultradeformable phospholipid transfersome vesicles (IDEA-070) has anti-inflammatory effects;[1] hence we assessed the efficacy and safety of IDEA-070 in inflammatory skin diseases, versus drug-free vehicle (TDT 070/sequessome vesicles). In this multicentre, double-blind, placebo-controlled study, patients (18–80y) with mild–moderate atopic eczema, dishydrotic hand eczema, plaque-type psoriasis, seborrhoeic eczema or acne vulgaris were randomised at a ratio of 2:1 to topical IDEA-070 (0.24mg ketoprofen/cm^2; n=167) or TDT 070 (n=82) spray b.i.d. for 3 wks. Across indications, 67.2% and 65.8% of patients in the IDEA-070 and TDT 070 groups, respectively, showed improvement in symptoms from baseline to wk 3 on a 7-point (0=clearance–6=worsening) Investigator Global Assessment (IGA; primary endpoint). Scores did not differ significantly between groups (mean 2.8 vs 2.6; p=0.29). Analysis of IGA scores by indication revealed improvement for both groups but no significant difference between treatments, except for seborrhoeic eczema for which TDT 070 surprisingly improved the IGA score at week 3 vs IDEA-070 (mean 1.6 [n=14] vs 2.7 [n=34]; p=0.015). The Patient Global Assessment score at wk 3 was also lower for TDT 070 among patients with seborrhoeic eczema (mean 2.0 [n=14] vs 3.0 [n=34]; p=0.02). Disease-specific assessment scores improved to a greater extent numerically with TDT 070 except for psoriasis. All treatments were well tolerated. Patients treated with IDEA-070 reported more local adverse effects vs TDT 070 (6.5% vs 1.2%). Both IDEA-070 and TDT 070 improved symptoms in >60% of patients with inflammatory skin disorders. However, IDEA 070 showed no significant benefit over drug-free vehicle TDT 070 which was even superior in the treatment of seborrhoeic eczema. The effect of TDT 070 observed in these exploratory analyses warrant further investigation in prospective clinical studies.[1]Lehmann et al. JAAD 2005;52:84. On behalf of the IDEA-070 Study Group.

956

Clobetasol solution, clobetasol in transfersome (IDEA-068) and the drug-free vehicle (TDT 068) all showed significant treatment effects in a randomised psoriasis plaque study

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Trans-dermal delivery of steroids in ultra-deformable phospholipid vesicles (transfersome) might avoid skin toxicity associated with conventional topical steroids; therefore, we assessed the efficacy and safety of clobetasol in transfersome suspension (IDEA-068) in patients with chronic plaque psoriasis. Patients (age ≥18; n=26) were enrolled in a single-centre, randomised, double-blind controlled study with intra-individual comparison of skin test areas and untreated skin. Three doses of clobetasol in transfersome (3.0 [D1], 1.0 and 0.3μg/cm^2), clobetasol in conventional solution (3.0μg/cm^2) and clobetasol-free vehicle (TDT 068/sequessome vesicles) were applied epicutaneously once daily for 3 weeks to areas of 2cm diameter on psoriatic plaques and healthy skin of each patient. Untreated plaque areas also served as a control. The mean change from baseline to week 3 in the Psoriasis Area and Severity Index (PASI) 2 total score (adjusted for untreated plaque area; primary endpoint) was smaller for IDEA-068 D1 vs clobetasol solution (1.15 vs 1.58; p=0.046). Of the doses of IDEA-068 tested, only D1 showed a statistically significant improvement in PASI 2 scores vs TDT 068 (mean change 1.15 vs 0.50; p=0.004). The improvement in unadjusted PASI 2 scores for TDT 068 was significantly greater than for untreated plaque areas (0.92 vs 0.42; p=0.004). Treatments were well tolerated with no skin irritation. Only 1 event (mild petechiae) was considered to be related to treatment (IDEA-068 D1). Skin atrophy (detected by sonography) was observed with IDEA-068 D1 and clobetasol solution treatment and was significantly greater for IDEA-068 vs TDT 068 (p<0.05). Collagen synthesis was more suppressed with IDEA-068 D1 and clobetasol solution treatment vs TDT 068 (p<0.01). IDEA-068 (3.0μg clobetasol) improved plaque size and severity, but failed to show superiority to clobetasol solution (trend to inferiority). The apparent effect of the drug-free vehicle TDT 068 warrants further evaluation.

957

Utility of eosinophil cationic protein levels in early diagnosis of intrinsic atopic dermatitis

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Background: Intrinsic type atopic dermatitis (ADi) is atopic dermatitis (AD) with low serum IgE and no allergen-specific IgE. There have been few laboratory markers to diagnose or evaluate the severity of ADi. Recently several reports have been published showing that eosinophil cationic protein (ECP) correlates with clinical severity of atopic dermatitis; however, report are scarce and controversial regarding the age-related changes and diagnostic utility of ECP in AD. Objectives: We aimed to compare clinical and laboratory parameters between ADi and extrinsic atopic dermatitis (ADe) and to assess the usefulness of ECP in diagnosing AD including ADi. Methods: A retrospective chart review was done on 178 patients 0-42 years of age diagnosed with atopic dermatitis. All patients were checked for total IgE, ECP and allergen-specific IgE with a thorough review of their medical history. Results: Mean age was 5.2±7.1 vs10.3±10.9 (p=0. 014) for ADi vs ADe. ADi had milder disease compared to ADe and less family history. ECP was elevated in both AD phenotypes. It was lower in ADi group (23.9±17.0) than ADe (56.2±107.9) but not statistically significant (p=0.10). There was a positive correlation between age and total IgE (r=0.504, p<0.0001), and between severity and total IgE (p=0.01). ADi patients under age two had significant negative correlation of ECP with age (r=-0.785, p=0.001). Conclusions: ECP can be considered an early marker of AD especially in very young children. High ECP value can assist in the diagnosis of infantile ADi.

958

Oral omega-3 PUFA apparently abrogates solar simulated radiation-induced immunosuppression in a randomised controlled clinical study

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Solar UVR is a key aetiological factor in skin malignancy. As omega-3 (n-3) PUFA protects against photoimmunosuppression and skin cancer in mice and is associated with reduced skin cancer risk in humans, we hypothesised that n-3 PUFA would abrogate photoimmunosuppression in human skin. The impact of oral n-3 PUFA on solar simulated radiation (SSR) -induced photoimmunosuppression in human skin was assessed using the nickel contact hypersensitivity (CHS) model. In a double-blind randomised controlled study, 79 volunteers (nickel allergic females, 22-60yrs, phototypes I/II) took 5g n-3 PUFA (70%EPA+10%DHA) or control lipid (medium chain triglyceride) daily for 12 wks. Post-supplementation, nickel was applied to 3 skin sites pre-exposed on 3 consecutive days to 1.9, 3.8 or 7.6 J/cm2 of solar simulated radiation (SSR), and to 3 unexposed control sites. Nickel CHS responses were quantified after 72h and % SSR-induced immunosuppression was calculated. Erythrocyte (RBC) EPA was measured using gas chromatography. SSR dose-related suppression of CHS responses was observed in both groups. Mean % photoimmunosuppression in the control group was 15% (95% CI 3.7,25.2), 21% (13.9,28.1) and 43% (34.9,50.8) at 1.9, 3.8 and 7.6 J/cm2 respectively, vs 8% (-0.5,16.7), 10% (2.3,17.9) and 40% (29.7,49.3) in the n-3 PUFA group, the difference between groups reaching statistical significance at 3.8 J/cm2 of SSR (11% (0.5,21.4), p=0.04). Post-supplementation RBC EPA was 4-fold higher in the n-3 PUFA vs control group (mean difference 2.69% (2.23, 3.14), p<0.001) confirming EPA bioavailability. Oral n-3 PUFA appears to abrogate photoimmunosuppression in human skin at low SSR doses, suggesting a potential mechanism for their reported chemopreventive activity.

959

Scleroderma-like cutaneous changes in association with taxanes

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Taxanes are a class of antineoplastic agents that disrupt microtubule function. Their activity has been demonstrated in advanced ovarian, breast, lung, bladder, and head and neck cancers. We report two cases of scleroderma-like cutaneous changes occurring after taxane administration, which has been reported only rarely to date. One patient received taxane chemotherapy for the treatment of metastatic breast cancer, and one patient for endometriod cancer. Diffuse edema of the distal extremities was noted first, followed by erythema and induration 8-12 months after the administration of taxane in both patients. Skin biopsies demonstrated dermal fibrosis consistent with scleroderma-like changes. Unlike systemic sclerosis, immunologic tests including antinuclear, anti-centromere, and antio-topoisomerase antibodies revealed no autoimmunity, and the patients had no Raynaud's or nailbed capillary abnormalities. Both patients had initial improvement with systemic corticosteroids. One patient, however, required the addition of methotrexate therapy upon steroid tapering for control of her disease. To our knowledge, this is only the second report of methotrexate being used for this refractory cutaneous side effect of chemotherapy. Although the etiology of scleroderma-like cutaneous changes due to taxanes has not been elucidated, it is important to consider this dermatologic toxicity in association with taxane chemotherapy.

960

Disruption of the elastic network and emergence of short tropoelastin-rich fibrils in striae gravidarum

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Striae gravidarum (SG) affect up to 90% of pregnant women. As SG pathogenesis remains unclear, we examined histologic and molecular changes in lesional skin, and hypothesized that elastic fibers are disrupted in SG that formed within 4-8 weeks prior to biopsy. Using light microscopy, we examined elastic fibers in van Gieson (VG)-stained skin sections (n=8 subjects). In control (hip) and stretched perilesional abdominal skin, the elastic network appeared intact. In SG, this network was severely disrupted, with patchy loss of normal fibers in the papillary and reticular dermis. In addition, many short, thin, haphazardly oriented "fibrils" were observed prominently in the reticular dermis. To investigate fibril composition, we used multiphoton laser microscopy to examine immunofluorescence staining of tropoelastin (TE, n=3). In SG, clusters of positively stained fibrils were randomly distributed, particularly in the reticular dermis, and appeared as thin fibrils by VG staining. Image analysis revealed that TE fibrils in SG occupied approximately 30-40% more dermal volume than staining of TE localizing to intact elastic fibers in control or stretched perilesional skin. In SG, cross-sectional width of TE fibrils was 1.9±0.2 μm, significantly less (p<0.05) than that of intact elastic fibers in the reticular dermis of control and perilesional skin (3.9±0.3 and 3.6±0.3 μm, respectively). TE fibrils persisted in SG for at least 6-8 weeks postpartum (n=3). Finally, to investigate the derivation of TE fibrils in SG, we measured gene expression of elastic fiber components. Compared with control, SG demonstrated increased expression of TE (12-fold), and fibrillins 1 and 2 (4.5 and 6.7-fold, respectively) (all n=8, p<0.05). Fibulins 1-5 showed no significant changes. These data indicate that early SG display disruption of elastic fibers and emergence of many short, separate TE-rich fibrils, which likely are the result of unsuccessful repair of normal fibers and contribute to SG laxity and persistence.

961

Adalimumab treatment optimization for psoriasis: Results of a long-term Japanese study

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Aim: To assess the long-term efficacy of adalimumab (ADA) and the response to dose escalation or de-escalation in Japanese patients (pts) with moderate to severe psoriasis following a phase 2/3, randomized, double-blind study (ClinicalTrials.gov number: NCT00338754). Methods: 142 pts with moderate to severe chronic plaque psoriasis, with a baseline (BL) psoriasis area and severity index (PASI) score of ≥12 or body surface area of ≥10%, entered an open-label (OLE) extension trial (NCT00647400) from the Phase 2/3 trial (NCT00338754). Pts received either 40mg or 80mg maintenance ADA every other week (eow). At week (wk) 52, pts receiving 80mg ADA dose de-escalated to 40mg ADA eow. Non-responders (defined as <50% PASI improvement) could move to 80mg ADA eow. Long-term efficacy (proportion of pts achieving PASI 50/75/90% reduction from BL PASI score) and response to dose escalation/de-escalation (50% PASI improvement) were measured up to 220 wks. Demographic factors affecting response to ADA were also determined. Last observation carried forward was used to impute missing data. Results: The PASI 50/75/90 achievement rates obtained for all pts, dose escalators, and de-escalators were 92.5%/81.0%/65.3%, 73.3%/53.3%/33.3%, and 96.2%/84.6%/67.3%, respectively. Similarly, PASI improvement rates observed for all pts, dose escalators, and de-escalators were 84.3±23.5%, 66.2±35.3%, 86.5±21.4%, respectively. The mean on-drug continuation rate was 77.9%±3.6% at 220 wks (Kaplan-Meier), with 3.5% (5/142) discontinuation due to inefficacy. Conclusions: Dose escalation and de-escalation may be beneficial treatment options for pts achieving an inadequate response or disease stabilization, respectively. Clinically meaningful efficacy of ADA for the treatment of moderate to severe psoriasis is sustained up to 4 years.

962

Risk factors for comorbidities among patients with moderate-to-severe hidradenitis suppurativa

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Introduction: Hidradenitis suppurativa (HS) is a chronic, recurrent, painful inflammatory skin disease, often underdiagnosed and undertreated. This post hoc analysis characterized the prevalence of common comorbidities associated with HS for patients (pts) in a 52-week, phase 2 trial of adalimumab (ADA) (NCT00918255) and the relationship between comorbidity prevalence and HS disease burden (high vs medium: HDB, MDB). Methods: Pts had moderate-to-severe HS (HS-Physician's Global Assessment [HS-PGA] ≥3). Hypertension (HT) was defined as treatment with anti-hypertensive medication and/or self-reported history of HT at baseline; depression as baseline PHQ-9 score ≥10; morbid obesity as baseline BMI >40 kg/m^2; HDB as baseline HS-PGA score >3 and/or Hurley Stage 3. Logistic regression compared prevalence among pts with HDB vs MDB; 95% Wald confidence intervals (CI) of odds ratios (OR) were generated. Results: Of 154 pts, the majority were women (71%), white (71%), <40 years of age (64%), smokers (ever; 70%), and had no family history of HS (72%) and MDB (61%). Mean (SD) age, 36 yrs (11.76); body weight, 97.2 kg (24.8). The 3 most common comorbidities from self-reported medical history were HT (21%), depression (18%) and obesity (15%). 10 pts (6.5%) had a history of diabetes mellitus. From medical examination, the prevalence of HT (uncontrolled elevated blood pressure) was 27%, morbid obesity 28% and depression 42%. Prevalence of HT was similar between pts with HDB (18%) and MDB (24%), OR [95% CI] 0.69 [0.310, 1.551]. Prevalence of morbid obesity was higher in pts with HDB (37%) vs MDB (22%), OR [95% CI] 2.01 [0.985, 4.114]. Prevalence of depression was higher in pts with HDB (52%) vs MDB (35%), OR [95% CI] 1.94 [1.004, 3.764]. Conclusions: HT, depression, and morbid obesity were relatively common comorbidities in this population, and a surprisingly high proportion of patients had diabetes. Pts with HDB were more likely to have depression and morbid obesity vs pts with MDB.

963

Chronic actinic dermatitis successfully treated with thalidomide

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Chronic actinic dermatitis (CAD) is a photodermatitis characterized by a pruritic, eczematous eruption on sun-exposed skin and photosensitivity with decreased minimal erythema dose to UVB, UVA, and/or visible light. Histology is consistent with chronic eczema. CAD is often seen in white males between 40 to 80 years of age and can be preceded by contact dermatitis, drug-induced photosensitivity, polymorphous light eruption, or less often HIV. Treatment is challenging and a standard therapeutic protocol does not exist. We present a case of a 55-year-old black man with a photodistributed pruritic, eczematous eruption for 40 years, initially prompted by photosensitivity to phenobarbital. Although the medication was discontinued, the eruption persisted with exacerbations mostly during the spring and summer. A diagnosis of CAD was made many years later based on clinical findings of scaly, lichenified plaques on sun-exposed skin with absence of discrete nodules, and histology demonstrating chronic eczematous changes with lymphoplasmacytic infiltrates. Laboratory studies were negative for HIV and urine porphoryins. Initial treatment included hydroxychloroquine, strict photoprotection, and topical steroids without benefit. Given the lack of response, thalidomide 100 mg daily was administered. Within two months, he had complete clearance and pruritus ceased. No adverse effects occurred. To our knowledge, this is the second report of recalcitrant CAD successfully treated with thalidomide. Unique features in this case include early age of onset and darker skin type. The exact mechanism of action of thalidomide is unknown, however, it is thought to exert immunomodulatory and anti-inflammatory effects. Based on the dramatic improvement seen in our patient, and in the case previously reported, we propose that thalidomide should be considered early in the treatment of recalcitrant CAD.

964

An observational, prospective study of monthly adalimumab therapy for disease maintenance in psoriasis patients: A possible new therapeutic option for good responders to the initial induction treatment

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Background: While adalimumab is a mainstay of treatment for moderate to severe chronic plaque psoriasis, the data regarding optimal treatment intervals for therapeutic maintenance are limited. Objective : We compared the clinical efficacy of biweekly maintenance administration of adalimumab with that of monthly treatment. Methods: 17 psoriasis patients treated with adalimumab 40mg every other week with initial loading dose of 80mg until week 24 were assigned to the maintenance therapy with adalimumab 40mg either every other week (n=7), or ebery month (n=10). The treatment efficacy was evaluated by the proportion of patients who achieved PASI 75 from the baseline at weeks 36, 48 and 60. There was no selection bias between the two groups. Results: At week 24, all the patients except for one in each group achieved PASI 75. In both groups, all the patients who achieved PASI 75 at week 24 maintained PASI 75 responses at week 60. Regarding two patients who did not achieve PASI 75 at week 24, one biweekly treated patient experienced a gradual increase in therapeutic response while one monthly treated patient showed exacerbation after week 24. Conclusion: Monthly adalimumab treatment seems to be a reasonable treatment option for patients who responded well to initial standard adalimumab treatment for 24 weeks. Since there are several limitations in this study, including the number of patients, observation period, and patients' characteristics, large randomized controlled trials are needed to confirm these results.

965

Tofacitinib ointment efficacy and biomarker improvement in psoriasis

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Topical and oral forms of Janus kinase (JAK) inhibitor tofacitinib (CP-690,550) are being developed for plaque psoriasis therapy. In a double-blind Phase 2a study (NCT01246583), 71 mild-moderate psoriasis subjects randomized to 2% tofacitinib Ointment 1 (O1 n=23), Vehicle 1 (V1 n=13), 2% tofacitinib Ointment 2 (O2 n=25), or Vehicle 2 (V2 n=10) applied study drug BID for 4 weeks (wk) to a single 300 cm^2 area containing a target plaque. Primary endpoint was Target Plaque Severity Score (TPSS) % change from baseline (BL) at Wk4. Secondary endpoint was patient-reported Itch Severity Item (ISI) change from BL. Statistical difference for Ointment vs Vehicle was shown if the 90% upper confidence limit (UCL) was <0 (*). Voluntary target plaque biopsy was done at BL and Wk4 (O1 n=5, V1 n=3, O2 n=5, V2 n=4) for exploratory biomarker immunohistochemistry (IHC) analyses. TPSS least squares mean (LSM) % change from BL was significant for O1 (-54.4%) vs V1 (-41.5%; delta -12.87; UCL -0.71*) at Wk4, as well as Wk2 and Wk3. O2 (-24.2%) did not separate from V2 (-17.2%; delta -6.97; UCL 6.62) at Wk 4 or any time. ISI LSM change from BL was significant for O1 (-2.92) vs V1 (-1.79; delta -1.13; UCL -0.09*) at Wk4, as well as Wk1. O2 (-2.12) did not separate from V2 (-1.09; delta -1.02; UCL 0.14) at Wk4 or at any time. At the subject level, O1 and V1 efficacy (TPSS & ISI) improvement from BL to Wk4 was generally associated with a decreasing trend in epidermal and dermal pSTAT3 and Ki67 IHC+ staining cells. Similar subject level association of O1 and V1 efficacy improvement with a decreasing trend in epidermal K16 and CD3 and dermal CD3 IHC+ staining cells was not observed nor was it apparent for O2 and V2 with any of the 4 biomarkers. In this small study, an ointment formulation of JAK inhibitor tofacitinib demonstrated improvement in psoriasis clinical signs and itch, which was supported by decreases in skin biomarkers.

966

Refractory dermatitis herpetiformis

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Background. Dermatitis herpetiformis (DH) is a blistering manifestation of coeliac disease which is treated with dapsone and life-long gluten-free diet (GFD). Refractory cases not responding to GFD treatment and often developing lymphoma are known in coeliac disease. Therefore, we examined our DH cohort for refractory cases, i.e. those DH patients who are unable to significantly reduce dapsone although they have adhered to a GFD for at least 3 years. Material and methods. Our DH cohort sampled from 1970 included 476 patients of whom 391 were alive. A questionnaire including questions about use of the dapsone, strictness of GFD and chronic illnesses were sent to these patients and 311 (80%) responded. Results. 98% of the DH patients adhered to a GFD and only 8% needed dapsone to control the rash. Among these were 12 (3.9%) refractory cases (9 men, 3 women), who still needed a significant amount of dapsone. Their mean age at diagnosis was 39 (range 19-66) years. The mean daily dose of dapsone was at diagnosis 70 mg (range 300-25) and at present 50 mg (75-12.5). The DH patients had been on a GFD treatment a mean of 12 (3-31) years. GFD was strict (no failures) in 8, failure once in every 2-3 month in 3 and failure once a week in 1 patient. At diagnosis, small intestinal biopsy showed subtotal villous atrophy in 4, partial villous atrophy in 5 and normal mucosa in 1 patient which is similar finding than in the other DH patients. Five refractory DH patients had a biopsy on a GFD and all showed mucosal response to the diet treatment. Two patients had associated hypothyreosis. Conclusions. The present study from a large DH cohort documents a small percentage of refractory cases, i.e. patients whose rash do not respond adequately to the GFD treatment. This refractory DH is dissimilar from refractory coeliac disease because gut mucosa seems to respond to the GFD treatment and no lymphomas developed.

967
WITHDRAWN

968
The proportion of Foxp3+ and IL-17+ cells in psoriatic skin

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Psoriasis is an autoimmune related chronic inflammatory skin disease that associated with Th17 cells which release interleukin-17 (IL-17) and IL-22. And regulatory T cells (Treg) are considered inhibitors of autoimmune responses. Therefore, the balance between regulatory and effector functions is essential for maintaining immune responses. But a recent in vitro study revealed a cell population that differentiates into helper T cells from Foxp3+ T cells, which develop after transient Foxp3 expression induced by cytokine signals and environmental factors. Foxp3+ T cells have inhibitory activity in human psoriatic lesions, and might also develop into helper T cells, like a double-edged sword. In this study, we analyzed Treg and Th17 in skin lesions with the relevant antibodies and examined their relations to the severity. Skin lesions from 5 psoriasis patients (3 men, 2 women) were examined. In previous report, we have reported that the number of Foxp3+ cells is correlated to Psoriasis Area Severity Index (PASI). It was suggested that when the inflammation is strong, these cells are increased. We examined the proportion (%) of Foxp3+ and IL-17+ cells in CD4. PASI score was negatively correlated with the proportion of Foxp3+ cells (r=-0.981), and IL-17+ cells (r=-0.966) among CD4. And the proportion of Foxp3+ CD4 T cells and IL-17+ CD4 T cells have positively correlated (r=0.911). In addition, the proportion of IL-17 among CD8 were fewer than IL-17+ CD3 T cells in lesional skin. Based on this study, lesional Foxp3+ CD4 T cells might be related to psoriatic activity by differentiating into Th17. It is possible that IL-17 might be produced by γδ T cells in psoriasis lesion.

969
Sunscreen titanium nanoparticles penetrate stratum corneum in human skin

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Sunscreens containing nano-sized particles like titanium dioxide (npTiO2) or zinc oxide are now widely in use. The nanoparticles in sunscreen products mostly exist as agglomerates, thus larger than the individual particles. There is a concern that sunscreen nanoparticles may penetrate skin, reach systemic circulation and cause harm to humans. Uptil now, experimental studies have not given firm indication that npTiO2 penetrate intact skin layers beyond the stratum corneum. Even when applied on compromised skin like sunburned or inflamed skin significant penetration has not been reported after investigations by several authors. There is a need for further studies on penetration in human skin in vivo. The aim of the present study was to examine penetration of npTiO2 in a commercially available sunscreen in human volunteers following applications in both intact and sunburned skin. Two human volunteers were studied under two different conditions: intact skin and sunburned skin (UVB, 0.4 J/cm2). Under both conditions sunscreen was applied (2 mg/cm2) on the back at an area of 20x30 cm. The sunscreen was applied 6 times a day, for seven consecutive days during both conditions. 2.5mm skin punch biopsies were analysed with Scanning Electron Microscopy, Transmission Electron Microscopy and energy dispersive X-ray spectroscopy. The biopsies were cut in 70 nm slices in a down-up direction in order to avoid sample contamination during handling. Ten to twenty nm electron dense particles containing titanium and aluminium were observed on the surface of the epidermis in the biopsies from skin where the sunscreen was applied. Similarly, in applied intact and sunburned skin particles were detected in layers beneath stratum corneum, i.e. in the stratum granulosum and stratum spinosum. In this study on human volunteers we have detected TiO2 nanoparticles in the epidermis beneath stratum corneum after applying a sunscreen for seven days to intact skin and to UVB sunburned skin.

970
Human sweat pores studied using CARS microscopy *in vivo*

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Sweating as a thermoregulation process of the body is an important function of the skin. Sweat pores are widely distributed all over the body and can secrete from 0.5 to 3 litres per hour depending upon the level and type of stimulation [1]. Hyperhydrosis or excessive sweating is a common problem affecting many people. Antiperspirant agents such as aluminum salts are widely used to control excessive sweating for personal hygiene purpose. These products tend to prevent sweat from reaching the skin surface [2]. In this work, we applied a non invasive imaging technique, Coherent Anti-Stokes Raman Scattering (CARS) [3], to study in vivo the sweating process and the effect of antiperspirant active ingredients. Compared to other techniques such as Optical Coherence Tomography (OCT) [4], CARS microscopy has a number of advantages such as (i) high-resolution three-dimensional imaging of a single sweat pore and (ii) chemical specificity. Using CARS, we investigated the distribution of anti-perspirant crystals on human palm and probed their spreading within depth or onto the surface of the sweat pore. The structure of sweat glands was completed using the two-photon fluorescence technique. We demonstrated that the anti-perspirant crystals when topically applied were mostly located on the border of the sweat pore (see Figure 1). Finally, applying oil onto the skin surface allowed pores being oil-filled which, as contrasting agent, offered the opportunity to follow-up the excretion of sweat droplets through oil under physical stimulation.

971
Quantitative assessment of clinical and histological differences in atrophic and hypertrophic photoaging

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We set out to quantify clinical and histological differences between two forms of photoaging. Subjects with clinical features of atrophic (AP) (n=19) and hypertrophic (HP) (n=23) aging and controls (n=11) enrolled in a case-control study with clinical assessment, photography, skin biopsies and a questionnaire. Group comparisons were assessed using one-way ANOVA for continuous variables and the Kruskal-Wallis test for ordinal variables. On a photonumeric photoaging scale, the mean score in AP was 5.47 compared with 6.78 in HP (p=0.011). No significant difference was noted between AP and controls (mean=4.55). HP scores were greater than controls (p=0.001). AP had a mean of 8.8 actinic keratoses compared to 1.2 for HP (p=0.001). Coarse wrinkling was severe in 70% of HP compared with 0% in AP (p<0.0001) and 9% in controls (p<0.0001). Sallowness was severe in 35% of HP compared with 0% in AP (p=0.005). Skin thickness was thin in 79% of AP compared to 35% of HP (p=0.037). Telangiectases in AP were severe in 32% of cases compared to 4% in HP (p=0.006). No significant differences in dyspigmentation measured by chromameter were noted between AP and HP. AP had moderate or severe dyspigmentation in 72% compared with controls at 27% (p=0.023). HP and AP had similar total collagen content by HPLC, and HP had significantly more total collagen compared to controls (2.1-fold, p=0.036). At the histological and ultrastructural levels, collagen fibril fragmentation and disorganization was comparable between AP and HP. In contrast, HP were characterized as having more widespread elastotic damage than AP (p=0.012) or controls (p=0.0003) (e.g., numerical scores of 3.5+0.6 v 2.5+ 1.2 v 1.9+0.7 in the three groups respectively). Sun exposure history and occupation had no significant influence on the type of photoaging. In addition to clinical distinctions, negative correlation between solar elastosis and AKs raises the possibility that AP and HP develop as a result of fundamental differences in the skin's responses to UV irradiation.

972
Measuring a sustained reduction in scalp Malassezia.spp following treatment with zinc pyrithione shampoo

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Characterized by the formation of visible flakes, the cosmetic condition known as dandruff has many contributing factors including the predisposition of the individual to the condition, the integrity of the stratum corneum skin barrier and the presence of cutaneous yeasts of the genus Malassezia. The widespread and effective use of antifungal treatments, including zinc pyrithione, in the control of cosmetic dandruff serves to illustrate the importance of Malassezial yeasts in the onset and resolution of the condition, however, despite this insight any precise elucidation of the mechanism by which Malassezia elicit a flaking response amongst susceptible individuals has thus far eluded science. In order to investigate the long term, between wash, protection benefits of antidandruff shampoo the present study recruited 50 men and 50 women (Shanghai, China) and subjected them to a single wash with either a standard beauty shampoo or an antidandruff shampoo containing zinc pyrithione. PBS buffer scrub samples were collected two days prior to washing, immediately after washing and at two, four and six days post wash. The buffer samples collected were then subjected to RT-qPCR analysis in order to accurately quantify the in-vivo effect of shampoo washing on the abundance of scalp relevant Malassezia. The results demonstrate an initial decrease in Malassezial numbers that is comparable between both beauty and antidandruff treatments. However after washing the numbers of Malassezia in the beauty cohort quickly return to baseline levels whilst the reduction in Malassezia seen in the zinc pyrithione treated cell was maintained for up to six days after washing indicating that antidandruff shampoos deliver a superior and long lasting anti-fungal benefit when compared to a commercial beauty shampoo.

973

Aspects of facial contrast are cues for age and health perception

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Facial appearance is critical for judgments we make about other people. Young and healthy-looking is considered attractive and looking younger than one's age is a sign of good health and longevity. Maintaining a youthful and healthy appearance is of great importance for many people. The aim of this research is to extend the list of cues used to perceive age and health. We tested whether facial contrast – luminance and color differences between the facial features (e.g. eyes, lips and eyebrows) and the surrounding skin – decreases with age and is related to perceived facial age and perceived health. We also investigated the regions within the eyes (sclera and iris) as their color influences the contrast of the eye region. Using a set of faces of 289 Caucasian women aged from 20 to 69, we measured the facial contrast and the iris and sclera contrast in CIELab color space. We observed a significant decrease with age for several aspects of facial contrast (e.g. luminance contrast of eyebrow region, redness contrast of the mouth region, yellowness contrast of the eye region, etc…) and significant changes for sclera in all three channels, due primarily to the appearance of the sclera becoming darker, redder, and yellower. These changes in the sclera contribute to reduce facial contrast with age. Individual faces were perceived as younger and healthier when these aspects of facial contrast were artificially increased, but older and less healthy when they were artificially decreased. The relationship between these aspects of contrast and apparent health was confirmed using a set of 150 faces of Caucasian women aged from 56 to 60. The faces with the healthiest appearance had higher contrast than the faces with the least healthy appearance. While contrast decreases with age and is a sign of poor health, this work suggests that one function of color cosmetics is to make a face younger and healthier and it has also clear application for practices of aesthetic procedures.

974

Mood disorders and suicidal ideation associated with 5-α reductase inhibitors: A RADAR report

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Finasteride (FIN) 1 mg/d is approved for androgenetic alopecia (AGA) treatment; FIN 5 mg/d and dutasteride (DUT) 0.5 mg/d are approved for benign prostatic hyperplasia (BPH) treatment. We evaluated reports in the FDA Adverse Event Reporting System (FAERS) for 5-αRI—associated depression (DEP) and suicidality (SUI) by calculating proportional reporting ratios (PRR) and empiric Bayes geometric means (EBGM) for relevant MedDRA codes. Through December 2011, we identified 54 reports of DUT-associated DEP and 324 reports of FIN-associated DEP of which 129 (40%) were 1mg dosing (likely for AGA). Mean age was 65.4 ± 12.3 years for DUT; 32± 10 years for FIN 1mg; and 65±15 for FIN 5mg. For SUI, there were 21 reports for DUT and 78 reports for FIN, of which 29 (37%) were associated with 1mg FIN. Mean age for SUI after FIN 1mg exposure was 35±10 (N=22) and 59±15 (N=24) for FIN 5mg; and 63.2 ± 16.5 years for DUT (N=11). For FIN-associated SUI, PRR=27.12 (95% CI 21.73- 33.85) and EBGM= 27.21 (95% CI 21.79-33.91). For DUT-associated SUI, PRR=15.55 (95% CI 10.15-23.84) and EBGM=15.59 (95% CI 10.11-23.28). For FIN-associated DEP, PRR=94.6 (95% CI 84.9-105) and EBGM=94.4 (95% CI 84.7-105). For DUT-associated DEP, PRR=39.19 (95% CI 30.09-51.12) and EBGM=39.09 (95% CI 29.47-50.52). Our analysis identified drug safety signals for suicide and suicidal ideation associated with exposure to 5-αRIs. Safety signals were detected at the higher dose typically used to treat BPH and also at the lower dose typically used to treat AGA. Current package inserts for finasteride and dutasteride mention depression but do not warn physicians and patients of risk of suicidality. Our findings add to existing evidence suggesting that 5-αRIs are associated with depression and also identify suicidality as a new safety signal.

975

The interpretability of the simplified psoriasis index: A practical tool for assessing psoriasis

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There is an unmet need for a reliable measure of psoriasis severity that is both easy to use and able to capture response to treatment. The Simplified Psoriasis Index (SPI) is derived from the Salford Psoriasis Index, a three-component tool for recording psoriasis severity, psychosocial impact and historical course: a novel composite severity score replaces the Psoriasis Area and Severity Index (PASI) and a self-assessment version for patients (saSPI) complements the professional version (proSPI). Previous studies had shown the acceptability, validity (n=100) and reliability (n=50) of both tools. This study investigated PASI-equivalent cut-off scores for the severity components of proSPI and saSPI (proSPI-s and saSPI-s) and the minimal important difference (MID) of each version. Severity scores obtained from 300 proSPI-s and 200 saSPI-s assessments were used to determine cut-off points, using the European Medicines Agency definitions of mild and severe psoriasis of PASI <10 and PASI ≥20 respectively. The MID, the smallest change to define responses meaningful to patients, was investigated in 73 patients who were followed at week four after starting a new treatment. Patients who achieved <50% and ≥75% reductions in PASI were defined as non-responders (<PASI50) and responders (≥PASI75) respectively. The Receiver Operating Characteristic (ROC) was used to analyse the PASI equivalent cut-off points and MID. Our study showed that proSPI-s and saSPI-s scores of <10 and ≥18 may both reasonably be used to indicate mild and severe psoriasis respectively (sensitivity and specificity >80%). Sixty-three percent reductions (83% sensitivity, 82% specificity) and 78% reductions (82% sensitivity, 70% specificity) in proSPI-s and saSPI-s respectively may be the smallest change to define responses meaningful to patients. The areas under ROC curve for all analyses were ≥0.8 indicating good diagnostic utility. While interpretability of PASI has never been systematically evaluated, both categorization and MID of SPI are now defined.

976

Pigmentary changes following photodynamic therapy with 5-aminolevulinic acid or methyl aminolevulinate cream

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Photodynamic therapy(PDT) has been used in the treatment of various benign and malignant dermatologic conditions. Several side effects such as erythema, hyperpigmentation, folliculitis, itching, and prickling were reported in the treated area after PDT. We sought to compare pigmentary changes in normal skin treated with 5-aminolevulinic acid(ALA)-PDT and methyl aminolevulinate(MAL-PDT) in Korean people with skin type III-IV over 6 months in a single-blinded prospective trial. In ten healthy volunteers, six skin areas on the inner part of one upper arm of each subject were treated with (A) ALA 20% in base cream without irradiation(IR), (A1) Metvix cream (MAL 16.8%) without IR, (B), (B1) control vehicles, (C) ALA 20% in base cream, (C1) MAL 16.8%, respectively. Areas B, B1, C, C1 were irradiated with a fixed dose of 37.5 J/cm2 at four hours after photosensitizer or vehicle application. IR was given 2 times at 1 week interval. The effects of healthy skin were evaluated by clinical, photographic and colorimeteric examinations. The skin pigmentation was graded by using the scale: 0, no reaction to 4, dark brown. We also measured L*a*b*, individual typology angle (ITA)* and ΔE*, quantitative and objective values to evaluate color changes. Results revealed that the control areas A, A1, B, B1 showed no significant change in skin color. In C and C1, 9 of 10 patients showed pigmentary change from 30 minutes after 1st IR and lasted about 6 months. Δa* values arised from 30 minutes after 1st IR and diminished rapidly at about 4 weeks after 2nd IR. ΔL*, ΔE*, ΔITA* values arised from 30 minutes after 1st IR and decreased slowly over 6 months. The maximum changes of ΔL*, Δa*, ΔE*, ΔITA* values were reached at 30 minutes after 2nd IR. Erythema and pigmentation in C were more prominent and prolonged than in C1. In conclusion, in subjects with skin phototype III-IV, pigmentation tends to last more than 6 months when cutaneous diseases are treated with PDT. The ALA-treated areas developed more severe erythema and pigmentation than the MAL-treated areas.

977

E-FABP is a predictive marker of clinical response to systemic treatment and ultraviolet therapy in psoriatic skin lesions

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Psoriasis vulgaris is a chronic skin disease. Objective assessment of psoriasis is difficult and new reliable biomarkers are needed. Recently, we reported that epidermal fatty-acid protein (E-FABP), an intracellular transporter of fatty acid, regulates keratinocyte differentiation and is expressed at high levels in psoriatic skin lesions. We analyzed levels of E-FABP in psoriatic patients by ELISA to evaluate its potential value as a monitor of disease activity. At first, serum E-FABP levels were measured in psoriatic patients and were not associated with skin condition. Next, E-FABP levels were measured in psoriatic skin-strippings. In healthy controls, E-FABP levels were similar in skin-strippings taken from every region except the face. In patients, skin stripping E-FABP levels were significantly higher in lesions than in uninvolved skin. The uninvolved skin of patients had higher levels than the skin of healthy individuals. These results suggest that a preclinical abnormality in fatty acid metabolism exists in patients. The relationship between the level of E-FABP in individual lesions and the local skin condition was assessed. Skin-stripping E-FABP levels showed a slight but significant correlation with the total erythema, induration and desquamation scores. It was indicated that skin-stripping E-FABP levels reflect local skin condition. We hypothesized that skin-stripping E-FABP levels may predict therapeutic efficacy, and we analyzed E-FABP during treatment (TNF-α inhibitors or narrow band ultraviolet B) . In cases with clinical improvement, E-FABP decreased 4–6 weeks after therapy but remained high or stable in cases that showed no clear improvement. The change in E-FABP levels in the first 4–6 weeks after therapy was tightly correlated with therapeutic outcome. Skin-stripping E-FABP appears to be a useful marker in psoriasis that could be used to monitor disease progression and treatment outcome.

978

Results of the UK dermatology clinical trials network's PATCH I trial: An RCT of prophylactic antibiotics for the prevention of cellulitis (erysipelas) of the leg in patients with recurrent disease

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Background: Cellulitis (erysipelas) of the leg is a common bacterial infection of the skin and underlying tissue. The PATCH I trial compared prophylactic low-dose penicillin with placebo for the prevention of recurrent cellulitis. Methods: Double-blind, randomised controlled trial (RCT) including patients with two or more episodes of cellulitis of the leg from 28 UK hospitals. Randomization was by computer-generated code, and 12 months of prophylaxis was allocated from a central pharmacy. Primary outcome was time to first recurrence. Participants were followed for up to 3 years. Because risk of recurrence was not constant over the 3 year period, the primary hypothesis was tested during prophylaxis only. Results: In total 274 patients were recruited. Baseline characteristics were similar for the two groups. During the prophylaxis phase, 30/136 (22%) of participants on penicillin had a recurrence compared to 51/138 (37%) on placebo (HR 0.55, 95% CI 0.35, 0.86; p=0.01), yielding a number needed to treat to prevent one further cellulitis episode of 5 (95% CI 4 to 9). During the no-intervention follow-up, there was no difference in the number of first recurrences (27% penicillin; 27% placebo). Overall, participants in the penicillin group experienced fewer repeat episodes than those on placebo (119 versus 164 respectively, Ptrend = 0.02). There was no difference in the number of related adverse events (37 penicillin, 48 placebo; p=0.50). Conclusions: In patients with recurrent cellulitis of the leg, penicillin is effective in preventing subsequent attacks during prophylaxis, but protective effects are lost progressively once stopped.

979

Non-invasive markers of liver fibrosis in patients with psoriasis taking methotrexate may not have sufficient accuracy to replace liver biopsy

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Methotrexate is an effective drug but is linked to the development of liver fibrosis. Liver biopsy, the current gold standard for diagnosis, carries significant morbidity. Here we used NICE methodology to systematically evaluate the evidence for the diagnostic accuracy of non-invasive tests of liver fibrosis in people with psoriasis on methotrexate using liver biopsy as the reference standard. 15 studies met the review criteria. Standard liver function tests (ALT, AST, ALP, GGT, Bilirubin, Albumin; 4 studies) had low levels of diagnostic accuracy: sensitivity (0-57%), specificity (63-100 %). Procollagen 3 propeptide (P3NP) (4 studies) showed wide variation in results: sensitivity (63-100%), specificity (64-98 %), positive likelihood ratio (LR) (1.93-36), negative LR (0-0.56). Only 2 of 4 P3NP studies provided strong evidence of clinical utility. Fibrotest (derived from alfa2-macroglobulin, apolipoproteinA1, haptoglobin, GGT, bilirubin; 1 study) similarly performed poorly: sensitivity (83%), specificity (61%), positive LR (2.14), negative LR (0.27). Imaging techniques had low sensitivities – liver radionuclide scans (3 studies): 50-83 %,) liver ultrasound (2 studies): 0-19 %,) elastography (1 study): 50 %. Limitations of the evidence included ascertainment bias; patients were selected due to deranged LFTs or cumulative methotrexate dose, so data may not apply to all patients with psoriasis taking methotrexate. Additionally, index tests were not compared to an identical reference standard due to a variety of pathological scoring systems. No single test performed well enough to replace biopsy. P3NP, which is widely used, fails to identify all patients with fibrosis and also has poor specificity. There is a lack of studies evaluating novel methods such as elastography. Accurate non-invasive tests are required to identify liver fibrosis given the importance of methotrexate in the treatment of psoriasis. Large, prospective studies in relevant cohorts using standardised histology scoring systems are required.

980

Link between innate and adaptive immune response in autoinflammatory condition of generalized pustular psoriasis

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Generalized pustular psoriasis (GPP) is a rare life-threatening disease characterized by recurrent episodes of systemic inflammation and erythematous pustular rash. It is thought to belong to spectrum of psoriasis, an HLA-class-I associated autoimmune disease. Meanwhile, the recent identifications of genetic defects in IL-36 receptor antagonist (IL-36RN), a physiological antagonist of IL-36 signaling, suggest the autoinflammatory pathomechanism with an excessive activation of the IL-1 pathway in GPP etiology (Marrkchi *et al* 2011, Onoufriadis *et al* 2011). In this study, we aimed to investigate how autoinflammation and autoimmunity contribute to GPP pathogenesis. Firstly, we identified two novel mutations of IL-36RN and particular HLA-molecules, which may be associated with the risk for GPP. Secondly, real-time PCR for cytokine expression and immunohistochemistry study confirmed local and systemic inflammation in GPP patients. Thirdly, increased susceptibility for proinflammatory signals significantly promoted auto-antigen driving T cell activation in T-cell stimulation assay using lymphocytes of patients. Finally, T cell receptor (TCR)-beta chain fragment length spectratyping and single cell TCR analysis were performed to detect strong oligoclonal T-cell expansions in skin and circulation. Collectively, innate and adaptive immunity cooperatively promoted T-cell mediated autoimmunity in autoinflammatory conditions. These results not only provide a link between innate and adaptive immune response in GPP pathogenesis, but also have important implication for therapeutic strategy of the disease.

981

A pharmacological model to evaluate the flush in rosacea patients

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The purpose of the presented work was to develop an experimental model to characterize the phenomenon of facial flush in 2 populations (non rosacea subjects and patients with rosacea) and test the ability of new chemical entities to inhibit the flush. 30 patients were included in the study (15 healthy volunteers, 15 erythemato-telangiectatic rosacea patients). Three stimuli commonly known to induce flush were used: hot Water (60°C, 200ml), tabasco (6 drops), sparkling wine (100ml, ~9 g of alcohol). Face microcirculation, temperature and color were measured for 1h15 (30 min baseline, 45 min post stimuli). Every 5 min the subject scored their sensation of heat on a 5-point numerical scale: 1, None; 2, Very Slight; 3, Slight; 4, Moderate; 5, Strong. Both populations experienced flushes but statistically significant differences were observed between Normal subjects and Rosacea patients on how high they rated their heat sensation (mean score 1.7 vs. 2.5 for hot water, 1.8 vs. 2.3 for tabasco, 2.4 vs. 3.4 for alcohol) as well as on the measure of their face microcirculation for water and tabasco. We conducted a second study to evaluate the repeatability of the model using hot water as the stimulus. 9 flusher rosacea patients out of 15 screened were selected. The procedure of flush induction was repeated at 3 different days. The patients flushed the 3 times and both their sensation and the modification of their face microcirculation were similar from one day to the other. In conclusion, the developed model was useful to characterize different components of the flush symptom in rosacea and seems to be a promising tool to test the potential of drugs to inhibit the flush.

982

Associations between rosacea subtypes and quantitative details regarding primary and secondary features of rosacea

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While subtyping of rosacea into 4 categories has been recommended (Standard Classification of rosacea; Wilkin et al., 2002), few studies have evaluated differences between rosacea subtypes in epidemiological and clinical features. The objective was to study associations between rosacea subtypes (ST), and quantitative and qualitative details regarding primary and secondary features of rosacea. Single center cross-sectional survey of a cohort of rosacea subjects recruited from a North German community. Rosacea subtyping was performed by a dermatologist who categorized subjects into ST1 (erythematotelangiectatic); ST2 (papulopustular); ST3 (phymatous) and/or ST4 (ocular). A total of 135 rosacea subjects were enrolled. Overall, 64% were ST1 and 36% ST2; 24% were also ST3 and 36% ST4. ST3 was three-fold more frequently associated with ST2 than ST1 ($p = 0.0002$). ST2 subjects more frequently reported the following symptoms associated with flushing episodes: burning (41% versus 17% for ST1; $p = 0.018$), skin tension (59% versus 26% for ST1; $p = 0.005$), and itching (17% versus 3% for ST1; $p = 0.027$). ST2, compared to ST1, was significantly associated with facial burning/stinging, phymas and edema. ST1 was more frequently associated with dry facial skin. Flushing (transient erythema) was reported by 66% with mean frequency of 5.5 times weekly and mean duration of 1.1 hrs. Sites most frequently involved by flushing were: cheeks, nose, neck, chin and forehead. Papulopustules were evanescent in 42% with mean remission duration of 3.0 months. Significant differences exist between ST1 and ST2 in rosacea-associated features. ST2 was more frequently associated with ST3. In conclusion, the findings in this survey are unique in characterizing the temporal features and duration of flushing and papulopustules; differences between ST1 and ST2 in rosacea-associated features; and differential associations between subtypes.

983

Subtype progression in rosacea: A retrospective survey of a rosacea cohort

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Rosacea is an enigmatic condition of unclear pathogenesis presenting as a chronic persistent facial dermatosis. For the purposes of research and clinical reference, it has been divided into 3 cutaneous subtypes (ST 1-3; erythematotelangiectatic, papulopustular and phymatous, respectively) and an ocular subtype (ST 4). The natural history of rosacea is unknown. The concept of rosacea progression between subtypes (STs) has been previously implied but not formally studied. Our objective was to evaluate the potential for progression of rosacea between subtypes. Rosacea subjects completed a survey regarding onset of rosacea-associated signs and symptoms. For the 113 rosacea subjects in this study, mean duration of rosacea was 21 years. For those with ST1, 31% also fulfilled criteria for ST2 at some time in the course of their disease while 69% did not. Of the former, 66% developed ST1 before ST2. Additionally, for those with ST1, 20% also fulfilled criteria for ST3 at some time in their disease while 80% did not. In those who did, 92% developed ST1 before ST3. For ST2 subjects, 34% also fulfilled criteria for ST3. Of the latter, ST2 developed prior to ST3 in the majority (83%). Ocular symptoms were reported by 35%, of which the majority developed after onset of rosacea-associated cutaneous features. This study suggests that a proportion of rosacea subjects progress from ST1 to ST2 and to ST3; and from ST2 to ST3.

984

The immunosuppressive role of dendritic cell subsets in untreated stage IV melanoma patients

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The role of dendritic cells in generating an immunosuppressive environment conducive to melanoma metastasis has not been fully elucidated. To ascertain dendritic cells, we identified 25 untreated stage IV melanoma patients and 25 healthy volunteers. To more accurately phenotype the dendritic cells all the studies were conducted with fresh whole blood samples within 6 to 8 hours of sample collection.The percent of lymphoid derived CD1c dendritic cells were significantly lower in the melanoma patients compared to the healthy volunteers ($p = 0.04$). Similarly for the myeloid derived CD303 dendritic cells a significant decrease was noted in the in the melanoma patients ($p = 0.0003$). We also evaluated the recently characterized cross presenting CD141 dendritic cells that were also significantly decreased in melanoma patients ($p = 0.02$). Interestingly following stimulation of dendritic cells with polyinosinic acid-polycytidylic acid (poly ic, TLR 3 agonist) no increase in expression of co-stimulatory markers CD80, CD83 or CD86 was noted in the DCs from melanoma patients when compared to healthy volunteers. The block in up-regulation of co-stimulatory markers in melanoma patients following poly ic stimulation may play an important in determining the mechanisms in generating systemic immune responses with a Th2 bias the is present in stage IV melanoma. In our study we have demonstrated a decrease in all dendritic cell subsets in fresh whole blood samples from untreated patients with stage IV melanoma. The lack of increased expression of co-stimulatory markers demonstrated in melanoma patients is important to consider when designing new systemic therapies for melanoma.

985

Clinical and histopathological features of IgG4-related skin manifestations in patients with IgG4-related disease

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IgG4-related disease (IgG4-RD) is a newly recognized systemic inflammatory condition characterized by mass-forming lesions with a dense lymphoplasmacytic infiltrate rich in IgG4-producing plasma cells accompanied by fibrotic or sclerotic changes. We have recently encountered two cases of IgG4-RD associated with skin manifestations with IgG4-positive plasma cells. It was found that including the present two cases, a total of five cases of IgG4-RD with skin lesions with IgG4-positive plasma cell infiltration were found in the literature. We analyzed skin lesions of these cases and revealed common clinical and pathological features of the skin lesions. The common features include: 1) localization near the main area of IgG4-RD involvement, such as the scalp, face, neck, auricle and postauricular region; 2) infiltration of IgG4-positive plasma cells and eosinophils in the dermis and subcutis; 3) skin lesions appeared after the onset of IgG4-RD (range from 2 months to 3 years). Based on these observations, we speculate that the skin lesions in these five cases are cutaneous manifestations of IgG4-RD rather than nonspecific IgG4-positive plasma cell infiltration and that the underlying pathomechanisms is related to that of the main IgG4-RD lesion. Our study suggests that IgG4-RD, especially those located in head and neck regions, may be associated with IgG4-related skin manifestations.

986

Narrow-band ultraviolet B treatment increases serum 25-hydroxyvitamin D and alters marginally cutaneous vitamin D metabolizing enzyme and antimicrobial peptide mRNA expression levels in psoriasis patients on oral vitamin D supplementation

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Background: Patients with psoriasis may have vitamin D insufficiency. A narrow-band ultraviolet B (NB-UVB) course heals psoriasis and increases significantly serum 25-hydroxyvitamin D (25(OH)D). Here we studied whether NB-UVB course improves vitamin D balance in the psoriasis patients who are supplemented with oral vitamin D. Methods: Twelve psoriasis patients (mean age 42.8 years) and 15 healthy subjects received oral cholecalciferol 20 μg daily. NB-UVB exposures were given three times in a week on the whole body. Serum 25(OH)D was measured by radioimmunoassay. From psoriasis lesions mRNA expression of CYP27A1 and CYP27B1, two enzymes needed for hydroxylation of vitamin D into its active metabolite, and antimicrobial peptides cathelicidin and HBD2 were measured. Results: At baseline serum 25(OH)D concentration was 74.14 ± 6.6 nmol/L in the psoriasis patients and 74.30 ± 14.8 nmol/L in the healthy subjects. Nine NB-UVB treatments increased 25(OH)D by 13.2 nmol/L (95% CI 7.2 to 18.4) and 17.0 nmol/L (CI 13.9 to 19.9), respectively. In psoriasis patients 18 NB-UVB treatments increased 25(OH)D by 49.4 nmol/L (CI 35.9 to 64.6). One month after NB-UVB treatment the increase was 29.9 nmol/L (CI 13.6 to 49.0). At baseline the psoriasis patients showed low CYP27A1 and CYP27B1, and high HBD2 mRNA expression levels compared to the healthy subjects. NB-UVB exposures decreased the expression of HBD2 gene. Conclusions: NB-UVB treatment increases significantly serum vitamin D concentration in psoriasis patients on oral vitamin D supplementation. Healing psoriasis lesions showed similar mRNA expression of vitamin D metabolizing enzymes and antimicrobial peptides than NB-UVB treated skin in the healthy subjects.

987

Efficacy and safety of indigo naturalis extract in oil in treating nail psoriasis: A randomized, observer-blind, vehicle-controlled, intra-subject trial

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Nail psoriasis treatment is notoriously difficult. While indigo naturalis has been demonstrated safe and effective in treating skin psoriasis, its effect on nail psoriasis has yet to be verified. This randomized, observer-blind, vehicle-controlled, intra-subject trial evaluates the efficacy and safety of indigo naturalis extract in oil (INEO) in treating nail psoriasis. INEO (experimental group) or olive oil (control group) was applied topically to the same subjects' two bilaterally symmetrical psoriatic nails twice daily for the first 12 weeks. From week 13 to 24, all subjects applied INEO to both hands. Of 31 subjects, 30 remained at week 12, and 27 at week 24. At week 12, comparing the experimental group to the control group, the mean percentage of reduction from the baseline single hand Nail Psoriasis Severity Index (NAPSI) was 49.8% (95%CI, 41.5%-58.1%) vs. 19.0% (95%CI, 10.2%-27.8%), and modified target NAPSI was 54.1% (95%CI, 41.9%-66.4%) vs. 17.3% (95%CI, 0.5%-25.1%), indicating that INEO was statistically superior to olive oil alone ($P < .0001$, $P < .0001$, respectively). The subject and physician's global assessments also showed similar results. There were no adverse events during 24 weeks of treatment. This trial demonstrates INEO is a novel, safe and effective therapy for nail psoriasis

988

Comparison of immunosuppressive cells and cytotoxic cells in cutaneous angiosarcoma: The development of novel supportive therapy for cutaneous angiosarcoma

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An imbalance of immunosuppressive cells and cytotoxic cells plays an important role in the tumor-bearing host. Immunosuppressive M2 macrophages, together with regulatory T cells (Tregs), play roles in maintaining the tumor microenvironment. In addition, we previously reported that about 80% of cutaneous angiosarcomas (CAS) were positive for MMP-9, which promotes the sprouting and growth of new blood vessels and also co-relates with immunosuppressive macrophages, such as myeloid derived suppressor cells (MDSC). The purpose of this study was to elucidate the involvement of immunosuppressive cells and evaluate the potencies of bisphosphonate, which was previously reported to suppress the expression of MMP-9, as a supportive therapy for CAS. We immunohistologically examined for the presence of Foxp3+ Tregs, CD163+ M2 macrophages and MMP-9+ cells as well as TIA1+ cells and granulysin+ cells in fixed sections of lesional skin from 6 cases with CAS treated with docetaxel alone or docetaxel and bisphosphonate. In all cases, numerous Tregs and M2 macrophages were present, while fewer granulysin+ cells or TIA1+ cells were detected. Interestingly, the overall survival was prolonged in the groups that received combination therapy (10 months vs 24< months). To further confirm the therapeutic effect of DTX with BPs, we performed Multi-Immuno Tox Assay (MITA) to examine unexpected immunological effects of the drugs. These findings suggest that the combining docetaxel with biphosphonate might be effective for MMP-9-expressing CAS by abrogating both angiogenetic factors and immunosuppressive factors in the tumor microenvironment, which might result in remission of the tumor after the standard therapy for CAS.

989

Development of OND-1, a safe cyclosporine analog as a hair regrowth drug

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With the knowledge that cyclosprin A (CsA) can induce human hair growth, the question arises whether CsA can be used therapeutically for patients with hair loss. Therefore, topically applicable and safe CsA analog deserves to be developed as a hair drug candidate. We have systematically explored whether it is possible to modify the CsA in such a way as to maintain its hair growth potency with reduced CsA toxicity. Among analogs, OND-1 was an equipotent anagen inducer, compared to CsA and retared catagen phase in the C57BL/6 mouse model. The LD50 for CsA when administrated intravenously and orally into ICR mice, was 214mg/kg and 1,854mg/kg, respectively while LD50 for OND-1 was >280mg/kg and >3000mg/kg. Toxic signs were apparent in CsA group; drowsiness,spasm, kyphosis,and piloelection while OND-1 group showed much milder signs.Since the kidney is a major target for CsA toxicity in man, the effect of CsA and OND-1 on specific kidney parameters and histopathological alterations were examined in detail. After 4 week oral treatment of 50mg/kg/day CsA SD rats showed a significantly more mineral deposition at the corticomedullary junction and tubular vacuolation, as compared to the 500mg OND-1. This nephrotoxicity was further supported by the marked rise of BUN and Creatine levels in the CsA group, while OND-1 caused statistically not significant rise in these parameters. Gene expression analysis of human hair follicle (HF) treated with OND-1 showed that most interestingly, OND-1 up-regulated a number of hair keratins and keratin-associated proteins known to be expressed in the HF. That transcription of these hair follicle keratins and associated proteins profoundly upregulated after a brief stimulation with OND-1 suggests that OND-1 impacts strongly on hair shaft proteins and thereby on hair shaft production. This study encourages to further explore OND-1, a safe CsA analog as the most interesting candidate and warrants human clinical trials for topical hair drug development.

990

Filaggrin-null individuals with and without eczema have a higher proportion of CD11c positive antigen presenting cells than wild type individuals

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Filaggrin (FLG) mutations are known to confer an epidermal barrier defect and are associated with atopic eczema (AE), yet the majority of individuals with FLG mutations have apparently normal skin. To investigate whether differences in immune function could be responsible for determining an inflammatory or non-inflammatory phenotype, we analysed antigen presenting cells by flow cytometry in skin blister roofs from FLG null individuals with and without AE and compared these with wild-type (WT) individuals. Cells which were viable, HLA-DR positive and CD1a positive were assessed for CD11c positivity. FLG null individuals without AE had the highest proportion of CD11c positive cells (60%) followed by FLG null individuals with AE (41%), WT individuals with AE (30%) and WT individuals without AE (20%) ($p=0.05$, Kruskall-Wallis). FLG null individuals without AE also had the highest proportion of CD11c hi cells (44%) followed by FLG null individuals with AE (34%) WT individuals without AE (17%) and WT individuals with AE (16%) ($p=0.01$, Kruskall-Wallis). While Langerhans cells are CD11c positive at low levels, HLA-DR+CD1a+ CD11c hi cells may represent inflammatory dendritic epidermal cells previously identified in atopic eczema. These cells have not previously been identified in FLG null individuals without AE. Differing populations of HLA-DR+CD1a+ CD11chi cells in individuals with FLG null mutations are an entirely novel finding and may provide an exciting link between abnormal skin barrier function and the development of an inflammatory phenotype.

991

Fibroblasts associated with terminal hairs in males are not protective against perioral wrinkling

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We previously reported that perioral wrinkling is more prominent in females than males, and that aside from age, smoking is also an independent risk factor for this clinical feature. In general, density of fibroblasts is greater around hair follicles (terminal > vellus) than in interfollicular dermis. Therefore, we hypothesized that increased terminal hairs in males than females in the perioral area and the associated increased number of perifollicular fibroblasts and their production of procollagen may be responsible for less perioral wrinkling in this gender. Eleven patients with moderate to severe photoaging (6F, 5M; age range 52 to 88) were enrolled and underwent biopsies of crow's feet and perioral skin. Mean wrinkling scores (0=none, 8=most severe) for females were 6.0 ± 1.8 (crow's feet) and 6.1 ± 0.9 (perioral) and for males 6.0 ± 1.5 (crow's feet) and 3.5 ± 0.7 (perioral). Immunohistochemistry was used to stain for prolyl-4-hydroxylase (surrogate marker of fibroblast) and procollagen I. Slides were coded without information on gender and biopsy location. All hair follicles were designated as terminal or vellus and assessed for marked (>50%) perifollicular procollagen I immunostaining. The number of fibroblasts was counted. In perioral skin, only vellus hairs were present in females and only terminal hairs in males. Perifollicular procollagen I immunostaining was seen in 64% of follicles in females and in 33% in males (p=0.44). In crow's feet region, the procollagen immunostaining intensity between females and males was also similar (p=0.83). Quantitatively, there were no significant differences in the number of fibroblasts between males and females (crow's feet [F=115, M=169; p=0.29] and perioral [F=62 and M=42, p=0.75]). The number of fibroblasts in smokers and nonsmokers was also comparable (p=0.82). Our data indicate that although hair types differ between males and females, the number of fibroblasts and their procollagen I synthetic capacity is similar and does not explain the gender difference in perioral wrinkling.

992

Analysis of protein expression *in-situ* using multi-spectral imaging is superior to conventional immunohistochemistry (IHC): A new paradigm for patient selection for targeted therapy

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The Nuance® multi-spectral imaging system consists of a light microscope equipped with a liquid crystal tunable filter, high-resolution digital camera and an image analysis software. It allows quantitative analysis of either single- or multi-label immunostained tissue sections or cytopreps. A multispectral wavelength signature is acquired for each individual chromogen (e.g. hematoxylin, diaminobenzidine, etc.) and sensitivity thresholds are established using appropriate positive and negative tissue controls. Images are then acquired from immunostained slides and the signal from each chromogen is recorded separately on a cell-by-cell basis. False colors can be assigned to chromogens to enhance their visual distinction. Data can be displayed in a variety of quantitative formats. Using this system, we assessed baseline expression of FAS (CD95) by CTCL lines. Quantitative results paralleled those obtained by flow cytometry. We then quantitatively monitored the upregulation of FAS by CTCL cells in response to methotrexate. We also used Nuance to determine the expression of CD30 in lesional skin infiltrates from 20 CTCL patients receiving therapy with brentuximab vedotin (chimeric anti-CD30 mAb + monomethyl auristatin E). CD30 expression varied widely among patients and among multiple lesions from individual patients. However, it was detected in all samples including low-level CD30 in 8/8 specimens judged to be CD30-negative by conventional IHC. The biological relevance of this low-level CD30 expression was underscored by significant treatment responses among some patients in this subgroup. Our findings demonstrate that multi-spectral image analysis is more sensitive than conventional IHC for detecting low-level antigen expression. This has major implications for patient selection for targeted therapy. In addition, its quantitative capabilities allow objective assessment of differential antigen expression.

993

Anti-TNF-alpha treatment reduces circulating Th22 cells and regulatory T cells, but does not reduce circulating Th17 cells in psoriasis patients

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Biologics made an impact on the treatment of psoriasis in recent days, the efficacy had been known by many reports. Recently, the pathogenesis of psoriasis is known for an imbalance of Th17, Th22 cells and regulatory T cells (Treg). Psoriasis lesions are produced with IL-17, IL-22 produced by Th17, Th22 or any other cells, psoriasis severity is related with Treg suppressive function. In this study, we evaluated the effects of Anti-TNF-alpha treatment on the Th17 and Th22/Treg balance in peripheral blood obtained from psoriasis patients treated with infliximab (n=53) or adalimumab (n=26) at five points (infliximab: baseline, 6w, 14w, 22w, 30w, adalimumab: baseline, 8w, 16w, 24w, 30w). Th17 (CD4+IL-17A+), Th22 (CD4+IL-22+IL-17A-) and Treg (CD4+CD25+Foxp3+) cells were analyzed by FACS. Serum IL-6 and TNF- alpha were significantly decreased to almost normal levels in infliximab (8.2±9.9 to 6.2±19.0, 18.9±27.1 to 8.9±9.9) and in adulimumab (20.8±63.5 to 2.4±5.0, 4.9±8.9 to 1.6±1.3), concomitantly with decreasing PASI score (22.9±12.5 to 7.3±9.1, 18.1±12.1 to 1.6±2.9). In infliximab patients, Th22 was significantly decreased at 14w (0.49±0.51%) than baseline (0.57±0.44%), in contrast, Th17 was significantly increased at 6w (1.26±1.41%), 30w (1.31±1.04%) than baseline (0.84±1.02%). In adalimumab patients, Th22 was significantly decreased at 32w (0.53±0.44%) than 16w (0.67±0.50%), Th17 was gradually increased. Treg in the infliximab patients was significantly decreased at 22w (3.8±1.7%) than 14w (4.5±1.7%), than in the adalimumab patients was significantly increased at 6w (4.8±1.9%) than baseline (3.8±1.4%), but decreased at 32w (3.2±2.1%). Moreover Th22 levels in the adalimumab patients were significantly inversely correlated with Treg levels (r= -0.619 p<0.01). These findings suggested that anti-TNF-alpha antibody treatment might be therapeutic effect by reduction of TNF-alpha and Th22 cells, but those might keep Th17 levels and reduce Treg levels.

994

Topical resiquimod therapy induces systemic immune activation and regression of both treated and untreated lesions in patients with CTCL: Early results of a phase I trial

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Previous in vitro studies have demonstrated that the TLR 7/8 agonist resiquimod can markedly enhance cellular immune responses in patients with advanced cutaneous T-cell lymphoma (CTCL). We initiated a phase I open-label trial of varying doses of topical resiquimod gel for the treatment of patients with stage IA-IIA CTCL. To date, 4 highly refractory patients (3 stage IB; 1 stage IIA) who had failed on average more than 6 previous treatments including IFN and oral bexarotene, applied 500 mg or less 0.06% resiquimod gel to up to 4 target lesions at varying frequencies for two 8 week cycles with a 4 week rest period in between. All patients experienced several days of low grade fever upon initiation of study drug, followed by decreased pruritus and clearing of treated target lesions as well as improvement in non-treated distant lesions. Analysis of peripheral blood demonstrated that therapy was associated with increased myeloid dendritic cell CD80 expression and NK cell CD107 expression, suggesting activation of both circulating mDC and NK cells. Analysis of T cells isolated from skin biopsies before and after treatment demonstrated that therapy was associated with intralesional influx of NK and cytotoxic CD8 T cells producing increased levels of IFNγ, perforin, granzyme and TNFα. The percentage of total CD4 T cells declined after therapy but effector functions of remaining CD4 T cells were enhanced, with increased production of TNFα, IFNγ and IL-17. Taken together, results suggest that topical resiquimod induces systemic immune activation, is highly efficacious in the treatment of refractory CTCL skin lesions and leads to regression of both treated and distant untreated lesions. The capacity of topical resiquimod to enhance systemic immune responses to cancer suggests it may be useful in other human skin cancers.

995

One-year follow-up of zoster-associated pain in 764 patients with acute herpes zoster treated using famciclovir

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Herpes zoster (HZ) represents an acute reactivation of varicella zoster virus and causes both blisters on the skin and severe neuralgia. HZ causes postherpetic neuralgia in 10-20% of affected subjects, but few large studies with long-term follow-up have been conducted. A cohort of 764 patients with acute HZ treated using 750 mg/day of famciclovir for 7 days and HZ-associated pain (ZAP) was followed monthly thereafter, until it disappeared for up to 12 months. Pain was evaluated using a numerical rating scale (NRS, 0-10) and patients received follow-up by telephone every month. Follow-up was completed for 751 (98.3%) of the 764 patients. Patients retaining pain reduced to 12.4% (85/688) by day 90, 6.9% (47/686) by 6 months, and 3.5% (24/683) by 1 year. Mean NRS remained at approximately 2 after 3 months. Stratified analysis revealed significant prolongation of the ZAP in: 1) elderly individuals (age >=50 or >=65 years; p<0.0001, log-rank test); 2) patients with moderate to severe skin symptoms at first visit (p<0.0001); 3) patients with severe pain at first visit (p<0.0001). Surprisingly, when stratified by dates after onset, earlier visitors (0-2 days after onset of eruption, n=262) showed a higher rate of ZAP than intermediate (3-5 days after onset, n=306) or late (6 days and later, n=119) visitors (p=0.016, log-rank test, period of 90 days). Further analysis of severity revealed a tendency for earlier visitors to show a relatively higher ratio of moderate/severe patients (45.4%) compared to intermediate (40.5%) or late (37.0%) patients (p=0.099, Cochran-Armitage test for trend). This study, with an exceptionally high tracking rate, revealed several new findings such as the delay between onset and presentation is affected by disease severity. Six ADRs were reported in 5 of 721 patients included in the safety analysis. Serious ADRs included two episodes each of vomiting and cramps.

996

CD164 and FCRL3 are highly expressed on CD4+CD26-T cells in Sézary syndrome patients

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Sézary syndrome (SS) represents a leukemic variant of cutaneous T cell lymphoma (CTCL) with circulating malignant CD4 T cells trafficking to the skin. The malignant cells express the cell surface molecules also found on normal CD4 T cells. Therefore, we attempted to find a specific marker for malignant cells that would distinguish them from normal cells. Comprehensive microarray analysis of gene expression in the patients' CD4 T cells indicated significantly increased levels of mRNA for cell surface marker CD164, a sialomucin found on human CD34+ hematopoietic stem cells, as well as FCRL3, a molecule present on a subset of human natural T regulatory cells. Both markers were increased in CD4 T cells from the SS patients compared to those from healthy volunteers, as also indicated by subsequent studies utilizing QPCR. Flow cytometry studies confirmed the increased expression of CD164 and FCRL3 primarily on CD4+CD26- T cells of SS patients. Importantly, a statistically significant correlation was found between an elevated percentage of CD4+CD164+ T cells and an elevated percentage of CD4+CD26- T cells in all tested SS patients (n=59) but not in patients with Mycosis Fungoides and atopic dermatitis or healthy donors. FCRL3 expression was significantly increased only in high tumor burden patients. CD4+CD164+ cells displayed cerebriform morphology and their loss correlated with clinical improvement in treated patients. Our results suggest that CD164 can serve as a marker for diagnosis and for monitoring progression of CTCL/SS and that FCRL3 expression primarily correlates with SS disease progression.

997

Long-tem efficacy and tolerance of an acne clarifying set for cleansing acneic skin

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A two part study evaluated an acne clarifying set including containing a sonic skin care brush, an extra soft brush head designed to be gentle for use on acneic skin, & a 2% salicylic acid cleanser for facial cleansing. Methods: 50 subjects with mild to moderate acne who were presently using acne cleansers participated in the 12 week, 4-visit home use study. In Part I of the study, non-invasive tolerance measurements were taken before and after 2 weeks of use from a subgroup of 38 subjects who cleansed their face at least once per day with test set over a 2-week period. The facial skin was assessed via measurements of Transepidermal Water Loss (TEWL), Skin Moisture/Hydration (H) and Erythema (E). In Part II of the study 50 subjects evaluated long-term efficacy after 12 weeks of use. Long-term efficacy was evaluated by a dermatologist via a global acne assessment scale (0-4) and self-assessment questionnaires. Results: Tolerance assessed after 2 weeks of home use showed no statistically significant increase ($p=0.77$) in E level indicating no irritation and no statistically significant change ($p=0.28$) in H indicating unaltered hydration/moisturization level, whereas TEWL measurements remained within the normal range for healthy skin indicating no disruption in to the skin barrier. Efficacy evaluated after 12 weeks of home use showed via the global acne assessment scale a statistically significant improvement ($p<0.01$) in acneic skin. Questionnaire data revealed: 92% of participants perceived the cleanser to be gentle on their skin for daily use, 80% felt their skin was hydrated after use, 88% saw a reduction in the appearance of excess oil by at least 60%, and a decrease in the frequency, duration and severity of their breakouts (89%, 88%, 80%; respectively) was noticed. Conclusion: The acne clarifying set is safe and effective for cleansing acneic skin.

998

Ethnic differences in skin irritation responses between caucasian and asian populations

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In evaluating the safety of cosmetic products or chemicals, it is important to assess susceptible ethnic population due to global marketing in cosmetic industry. The aim of this study was to investigate the ethnic variations (Asian and Caucasian) in skin irritation responses of several positive irritants. We performed patch test on the back with 0.5% Sodium lauryl sulfate (SLS) aqueous and 0.15% retinol prepared in 1,3-butylene glycol. We conducted the stinging test with the test materials in a 5% lactic acid aqueous and capsaicin prepared at a 0.001% (w/v) in 10% ethanol solution separately. Clinical tests was performed at 4 countries (Korea, China, France and USA). Our survey showed the similar incidence of self-perceived sensitive skin between 2 ethnic groups but the incidence of skin adverse experience by cosmetics in Asian subjects (33.0%) appears significantly high in comparison with Caucasian subjects (11.3%). Our data indicate that in standard positive irritant such as 0.5% SLS aqueous solution Asian subjects showed significantly higher scores than Caucasian subjects and in 0.15% retinol patch test Asian tends to appear somewhat higher than Caucasian. Our data also showed that neurosensitivity of Asian (Korean and Chinese) was higher than that of Caucasian for 5% lactic acid and 0.001% capsaicin. Consequently, even though self-reported skin sensitivity does not appear to differ according to ethnicity, there are ethnic differences of objective and subjective skin irritation response to several standard positive materials.

999

Correlation between age and skin elasticity, at different body sites. *In vivo* study

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As we age, skin gradually loses its elasticity, resulting in wrinkles and sagging. In order to trace the stages of these changes, we monitored in vivo, skin elasticity parameters with age at different body sites. For this purpose, 40 volunteers were assigned to one of five groups of 8 volunteers: 20-30; 30-40; 40-50; 50-60; and 60-70. Skin elasticity was evaluated by Cutometer® and Balistometer® on eight different body sites (cheekbone, neck, thigh, forehead, jaws, forearm, clavicle and temple). Comparing the two devices, we observed that the Cutometer gave better correlation with age compared to Balistometer. Indeed, for all the body sites measured, we obtained significant negative correlation for the three main Cutometer parameters (R2, R5 and R7). We noticed that the correlation depends on the body sites. The most significant correlation with age was obtained on the neck where we found a highly significant negative correlation with age, for the three parameters. (R2: $p<0.0001$; $r= -0.8595$ / R5: $p<0.0001$; $r= -0.8951$/ R7: $p<0.0001$; $r= -0.9119$). We also obtained signifucant negative correlation for the temple, the clavicle and the forearm but not for the forehead. These results showed that Cutometer us a very interesting device to evaluate the correlation between skin elasticity and aging on different skin site.

1000

Dermal stem cell plays an essential role in skin aging. *In vivo* study

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The dermis contains dermal stem cells which allow the maintenance, the repair and rejuvenative properties of the skin. They are intimely linked with the tensile and elasticity biomechanical properties of the skin. For this purpose, we designed a biofunctional that helps to maintain dermal stem cells, and we assayed in vivo its property to limit aging effects.The anti-aging effects of IV12001at 1% were determined, in vivo, by a double-blind study versus placebo. The skin elasticity was evaluated on the neck of 19 volunteers (aged 50 to 64 years) using a Cutometer®. They applied IV12001-containing and placebo creams twice a day on the neck and on the face during eight weeks. After, these eight weeks of application, we found a significant increase of R2 which is the main Cutometer parameters for assessing skin elasticity and aging, (it represents the gross elasticity of the skin). Moreover, a significative enhancement of two more parameters (R5 and R7) was noticed, which supported the previous results. The improvement of skin elasticity can be seen on the pictures of the crow's foot areas, where the wrinkles had faded, they appeared less deep with a smoother skin on the inducer-containing side. In addition, at the end of the study, 63.2% of the volunteers noticed an improvement of the wrinkles of the crow's feet areas on the IV12001 treated side against 47.4% on the placebo side. Concerning their wrinkles under the eyes, 57.9% of the volunteers observed an improvement on the treated side.To conclude, our compound, by its action on dermal stem cells in vitro allowed a better skin elasticity. The skin was visibly younger with better global appearance.

1001

Anti-BP180 NC16A antibody levels are useful in predicting disease outcomes in Asian patients with bullous pemphigoid

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Anti-BP180 NC16A antibodies play a key role in the pathogenesis of bullous pemphigoid (BP). The aim of this study was to correlate anti-BP180 antibody levels with disease severity, clinical course and outcome in a cohort of Asian patients with BP. This was a prospective cohort study conducted from 1 March 2005 to 31 March 2008 at the National Skin Centre, Singapore. 35 patients with newly-diagnosed BP were recruited. Disease activity was assessed using a standardized scoring system and serum anti-BP180 IgG was measured using ELISA kits at diagnosis, week 4, week 8, week 12 as well as at disease flares and remissions. Patients were treated according to a standardized treatment regime. 33 out of 35 patients completed the 12 weeks of follow-up. 25 were followed to 1st clinical remission. 27 had flares after week 12. Mean durations from diagnosis to first clinical flare and remission were 1.2 and 1.5 years, respectively. Mean duration of follow-up was 3.2 years. Correlations between disease activity and anti-BP180 IgG levels were: at diagnosis ($r=0.53$, $p=0.001$), week 4 ($r=0.38$, $p=0.033$), week 8 ($r=0.44$, $p=0.011$) and week 12 ($r=0.31$, $p=0.091$). A statistically significant correlation ($r=0.85$, $p<0.0001$) was observed during disease flare but not at remission. No association was observed between anti-BP180 IgG levels at week 12 and occurrence of disease flare or remission within 1 year. Hazard of remission after 12 weeks follow-up was 23.7% lower for every 1% increase per week in anti-BP180 IgG level from week 4 to week 12 ($p= 0.02$). Number of flares after clinical remission was reduced by 64% for patients with negative titres (<9 U/ml) at clinical remission ($p=0.02$). A cutoff of 37 U/ml in the ROC curve for anti-BP180 IgG level at diagnosis was predictive of flare within 2 years (area under ROC curve 0.885, sensitivity 89%, specificity 100%). Anti-BP180 IgG levels and their changes may be useful in predicting disease activity during disease flare, rate of clinical remission and likelihood of disease flares after clinical remission.

1002

Preservation of telomere integrity exhibits protecting effects under stressfull lifestyle condition. *In vivo* study

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Telomeres are natural protective regions of repetitive DNA at the end of chromosomes. The T-loop configuration of the single-stranded ends of chromosomes is stabilized by the proteic shelterin complex and hence is not recognized as damaged DNA. Maintenance of the level of shelterin proteins (such as TRF2, Telomeric-Repeat Binding Factor-2), and of telomere integrity is critical during skin aging and are influenced by lifestyle factors. Thus, we were interested in telomere protection and we designed a new compound (IV10.008) that targets Shelterin components in vitro. In the purpose of demonstrating the protective effects of IV10.008 against lifestyle factors, in vivo, we designed a two-month double-blind study during summer. 18 middle age volunteers participated in this study. They applied the IV10.008 or the placebo creams, twice a day, on their arms. After eight weeks of application, the IV10.008 compound helped limiting significantly summertime aggressions as it helped increasing skin hydration and improving the quality of the skin on the area of the arm. These results were confirmed at a microscopic level. Indeed, the VivaScope® results showed a preserved horny layer with a thickness thinner and a better cohesion of corneocytes for the IV10.008 treated side. Moreover, the damage generated by the summertime conditions, at the granular level were limited. The granular cell density significantly increased after IV10.008 application showing that cell division and organization were not altered by summertime conditions. In conclusion, the protection of telomere uncapping allows to limit skin damage caused by environmental condition and helps the skin to look healthier.

1003

The neurokinin 1 receptor is up-regulated in pruritic skin diseases

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The neurokinin 1 receptor (NK1R) has been lately discussed as a prospect candidate for antipruritic treatment. It seems that substance P as endogenous mediator of NK1R is a relevant pro-inflammatory mediator and mast cell activator in pruritic diseases and could be a key neuropeptide for pruritic skin diseases such as prurigo nodularis (PN) and atopic dermatitis (AD). The aim of this study was to determine the expression of the NK1R in the lesional, pruritic skin of patients with AD (n=13) and PN (n=13) compared to healthy controls (HC, n=10) using different methods (immunofluorescence (IF), real-time PCR, western blot). Women from 22 to 77 years (mean age: AD, 42 years; PN, 66 years; HC, 48 years) formed the studied group. In all patients NK1R was found mainly intercellular in the epidermis by IF staining. Compared to normal skin of HC, a more distinct signal of NK1R was observed in pruritic patients. A significant 2-fold down-regulation of the NK1R RNA level in AD ($p<0.01$) and PN ($p<0.01$) compared to HC was measured by quantitative real-time PCR analysis. On protein level, however the higher variants of the NK1R isoforms (> 50 kDa) show a significant up-regulation in the western blot signal of patients with AD ($p<0.01$), compared to HC. In the lower isoforms (< 40 kDa) no differences were detected within the groups. An intercellular epidermal up-regulation of NK1R could be detected in IF staining in the skin of patients with PN, who had been treated by the NK1R antagonist aprepitant for four weeks. This is the first investigation on the expression of the NK1R in AD and PN including an analysis before and after a therapy with a NK1R antagonist. These data indicate that NK1R is involved in pruritic diseases and represents a potential therapy target. Further investigations have to enlighten the particular role of epidermal NK1R in pruritic skin diseases.

1004

Triple antibiotic combination therapy may improve but not resolve granuloma annulare

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Granuloma annulare (GA) is fairly common yet lacks reliable treatment options especially when multiple lesions/dissemination exists. A recent case series reported clearance of disseminated GA in 6 patients treated monthly for 3 months with a combination of 3 anti-leprosy antibiotics, and we sought to expand on this in a prospective open-label study. Subjects aged 18-75 with ≥5 lesions of GA enrolled and received once monthly rifampin 600 mg, ofloxacin 400 mg, and minocycline 100 mg for 6 months. We derived a novel primary outcome measure to assess clinical response by calculating a Granuloma Annulare Severity Index (GASI) score. The GASI was calculated at baseline, and months 2, 4, and 6, and generates a set of 19 discrete ordinal numbers between 0 and 50 [GASI score = number of lesions x (average lesion color + average lesion height)]. 21 subjects enrolled (age 52±12 yrs, all women except one) and 15 completed all study visits. 6 terminated early because of treatment dissatisfaction (n=4) or were lost to follow-up (n=2), but all were included in the analysis. 10 subjects (48%) achieved at least a 50% reduction in their GASI, including 3 (14%) that reached 75% improvement and 1 (5%) that cleared. 6 subjects (29%) had no change or worsening of their GA. Median GASI scores decreased significantly by 15 points ($p<0.01$; median initial GASI 30, IQR 16 and median final GASI 15, IQR 20), although the clinical significance of this result is unclear as the median final GASI of 15 still represented significant disease. A conservative estimate of clear skin (>10 persistent lesions but light pink and macular) yields a GASI of 10 or less; excluding the subject that cleared, only 5 of 6 subjects (25% of the total cohort) had a score of 10 at 6 months and 1 (5%) had a score of 6. Our results suggest that once monthly triple antibiotic therapy may improve but not clear GA over 6 months of intervention. Perhaps encouragingly, however, the trend towards improvement might imply that a longer treatment duration, or perhaps an increased frequency of dosing, might be more beneficial.

1005

MIF in the stratum corneum as a biomarker of skin irritation

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Macrophage migration inhibitory factor (MIF), a pleiotropic inflammatory mediator, has been known to be upregulated in affected areas of skin irritation due to UV irradiation. In this study, we examined whether MIF in the human stratum corneum (SC), collected by tape-stripping, which is a useful non-invasive method, has potential value as a biomarker of skin irritation. Initially, in order to establish a method for measuring MIF from tape-stripped SC, the amount of MIF in a barrier-disrupted skin model was examined. One of the forearms of healthy female subjects (n=14) was washed with a 10% sodium dodecylsulfate (SDS) solution 5 times per day for 2 days. The other forearm of each subject was similarly washed with tap water as a control. Tape-stripped SC samples were collected over time (1–12 days) after the SDS treatment. Transepidermal water loss increased on the 1st day after SDS treatment, while MIF levels in the SC from SDS-treated forearms increased from 2 to 10 times, relative to controls, by the 12th day after treatment. Next, MIF levels in the SC were investigated following exposure to sunlight. Cheek SC samples were collected from healthy subjects before and after exposure to sunlight during leisure activities (sun-exposed group; n=10). The MIF levels in SC after exposure to sunlight increased on the 4th post-exposure day, compared to the levels prior to exposure. Finally, we examined the MIF levels in tape-stripped SC samples from the cheeks (sun-exposed area) and buttocks (non-sun exposed area) of healthy subjects (20–70 years old, n=32). The cheek SC had higher MIF levels compared to the SC from the buttocks ($p< 0.05$). These data showed that expression levels of MIF in the SC are increased in a sunlight-exposed area. Thus, these findings suggest that measurement of MIF from SC is a suitable biomarker for skin irritation related to skin barrier disruption and sunlight exposure.

1006

Vitality index as a new marker of skin ageing

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During ageing, cell senescence and dysfunction of the cell mitochondrial network are related to the skin cells bioenergy and their regeneration potential. The maintenance of cutaneous vitality, related to its faculty of regeneration, is essential for skin youthful aspect and its mechanical properties. Many studies recognize that the vitality of the face skin is also a key element for its beauty whatever the age. In order to quantify skin vitality, a new multifactorial mathematical model was defined. A clinical study was carried out on a panel of 216 Caucasian women aged 20 to 65 years old. 12 cutaneous criteria have been evaluated by a dermatologist according to a 10-point scale ranging from 0 to 9. The panel had an average BMI of 22.3 with 85.1% of the panel between 18 and 25. Furthermore, 10.9% of the women had oily skin, 9.8% normal skin, 58.6% combination skin and 20.7% dry skin. 2.3% of the panel was of phototype I, 35.2% of type II, 52.3% of type III and 10.2% of type IV. Following the dermatological evaluation, an analysis by linear regression and principal component analysis allowed to define the clinical criteria involved and their importance. A modelisation by using multiple regression allows the definition of an equation reflecting the skin vitality index Ei. The criteria selected are loss of firmness (f), loss of density (d), loss of radiance (r), the presence of wrinkles and fine lines (w), the lack of complexion homogeneity (h) and the loss of cutaneous elasticity (e). $Ei = 0.08f+0.21d+0.38r+0.10w+0.16h+0.06e$. Ei was determined for five-year-age groups. The fewer the flaws the lower the index is and the younger the skin looks. In complement of biophysical measurements, this clinical vitality index is used to measure the efficacy of anti-ageing creams.

1007

Toll-like receptor signaling induces serum amyloid A and IL-6 expression in patients with recessive dystrophic epidermolysis bullosa

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Secondary amyloidosis (SA), a critical complication caused by chronic inflammatory diseases such as rheumatoid arthritis (RA), is sometimes seen in patients with recessive dystrophic epidermolysis bullosa (RDEB). Serum amyloid A (SAA) is an essential factor in the pathogenesis of SA, and IL-6 is also considered an important cytokine because anti-IL-6 therapy is effective for SA. We observed that RDEB patients (n=11) have significantly higher level of SAA and IL-6 compared with healthy volunteers (n=10) or patients with atopic dermatitis (n=10) or psoriasis (n=10). In addition, a long-term (more than 5 years) follow-up of three RDEB patients revealed the persistence of the high level of serum SAA and IL-6. Next we hypothesized the skin could be a source of SAA and IL-6 in RDEB because the sources of them in RA have been considered not only the liver but also the joints. RDEB patients usually have widespread skin ulcers, and keratinocytes and fibroblasts surrounding ulcer lesions are persistently exposed to microbes due to lack of epidermal barrier. Therefore, we examined if these cells produce SAA and IL-6 through microbe sensors, Toll-like receptors (TLRs). The analyses by real-time PCR and ELISA revealed that ligands of TLR3 (poly I:C), TLR5 (flaggerin), and TLR2/6 (Malp2) significantly induced SAA expression in normal human epidermal keratinocytes (NHEKs). In normal human dermal fibroblasts (NHDFs), TLR1/2 (Pam3CSK4) and TLR2/6 ligands significantly induced SAA production. Similarly to SAA induction, IL-6 expression was also induced in both NHEKs and NHDFs. Furthermore, SAA itself induced SAA and IL-6 expression in NHDFs but not NHEKs. In addition, immunohistochemical analysis showed increases in SAA and IL-6 in skin ulcer lesions of RDEB patients. These results suggest that chronic skin inflammation through innate immunity might trigger the elevation of SAA and IL-6 in the sera of RDEB patients.

1008

The use of HF ultrasonography and 3D imaging system for treatment monitoring of striae distensae - preliminary report

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Striae distensae (stretchmarks) constitute one of the key problems reported by the patients visiting aesthetic medicine clinics. However, there is still a shortage of effective methods to monitor changes occuring during different treatments. In recent years, HF ultrasnography and 3D imaging system (PRIMOS) have increasingly become popular, which enables monitoring of skin lesions. The study sample encompassed 16 women with stretchmarks involving their thighs and buttocks. Female participants applied the anti-stretchmark cosmetic product on the involved skin for 4 weeks. The course of treatment was monitored using the HF ultrasound and 3D imaging system. EPISCAN ultrasound device equipped with the 50 MHz mechanical probe and PRIMOS were used for examination. All scans and images- pre- and post-treatment- were performed at the same location, at fixed setting of scanner's and camera's parameters. The following parameters were subjected to the ultrasound evaluation: epidermal echo thickness, dermis thickness and dermis echogenicity. Stretchmarks are clearly visible on HF ultrasound scans, although in case of mild striae imaging requires examiner's expertise and experience. No statistically significant differences were observed between the values of epidermal echo thickness and dermis thickness measured pre- and post-treatment. After treatment, the dermis echogenicity significant increased. PRIMOS analysis showed decrease in depth and volume of stretchmarks before and after cosmetic treatment. The high frequency ultrasound imaging technique and 3D imaging system are useful for striae imaging. In order to use HF utrasonography and 3D imaging system in efficacy assessment of anti-stretchmark therapies, further studies and development of uniform examination standards are necessary.

1009

Impaired barrier function, stress responses and signalling pathway changes induced by filaggrin knockdown in a skin equivalent model

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Mutations in filaggrin (FLG), resulting in reduced or loss of protein expression have been defined as a major cause of ichthyosis vulgaris and atopic eczema. FLG is a major constituent of the epidermal barrier providing mechanical strength through protein-lipid crosslinking and contributes to epidermal hydration through breakdown into natural moisturising factor. We investigated the consequences of FLG protein knockdown in a human epidermal equivalent model, using lentiviral transduction of shRNA that resulted in reproducible reduction of FLG expression by a mean of 90% (n=10, P<0.0001), compared to controls. Trans-epidermal water loss (TEWL) readings from the equivalents were increased 1.5 fold in the FLG knockdown equivalents compared to the controls; correspondingly there was a 2 fold increase in TonEBP (NFAT5) expression, a nuclear transcription factor induced during hypertonic stress, in FLG knockdown equivalents. Microscopic examination of cornified envelopes (CE) purified from the equivalents, revealed increased CE disruption in the FLG knockdown compared to the controls following 5 min water bath sonication. No compensatory increase in protein expression of other keratinocytes differentiation markers, CK10 and loricrin, was observed in FLG knockdown equivalents compared to controls. However, proteomic analysis of equivalents delineated changes in pathways associated with stress (HSPE1), immune responses (galectin-3 binding protein), mTOR signalling and transport (FABP5). Notably, a number of these pathways corresponded to those previously identified in transcriptome analyses of atopic eczema skin. These data underscore the role of FLG in epidermal barrier function and identify novel pathways activated by FLG deficiency, similar to those seen in atopic eczema. Our FLG knockdown model shares many characteristics with atopic eczema/ichthyosis vulgaris epidermis suggesting potential utility of the model for therapeutic discovery.

1010

The efficacy assessment of mature skin cosmetics using the HF ultrasound

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In recent years, HF ultrasonography has been increasingly more commonly used for skin assessment and monitoring of different therapies in cosmetology and aesthetic medicine. It is a relatively inexpensive method, reproducible and safe for the patient - which explains its chance for being widespread. The purpose of research was to assess the efficacy of mature skin cosmetic using the HF ultrasound imaging. 22 women were enrolled, aged 58 to 70 years (the medium age was 63.7 y.o.). The enrolled women applied day and night cream for mature skin for 4 weeks. The ultrasound skin evaluation was performed twice - prior to treatment (at baseline) and after the treatment. The HF ultrasound device EPISCAN, equipped with the 50 MHz mechanical probe was used for the examinations. All scans were performed at fixed setting of the scanner's parameters and at the same locations: a cheek and a forehead. The following parameters were subjected to the ultrasound evaluation: epidermis echo thickness, dermis thickness, dermi echogenicity and separately the echogenicity of its inferior (reticular) layer. After use of cream, a statistically significant increase in demis echogenity was observed, for the measurements performed on the cheek close to the nasolabial sulcus. Also, the statistically significant differences were observed in the echogenicity of the inferior layer of dermis, for the measurements taken on the forehead, which may be suggestive of collagen fibre restoration. Furthermore, the dermis thickness increased following the use of creams. However, this difference was not statistically significant. The changes visible on the HF ultrasound scans correspond to the visual improvement of skin appearance reported by the patients and observed under palpation. HF ultrasonography enables monitoring of skin changes occuring as a result of using different cosmetic products, thus making possible their efficacy assessment.

1011

Rising educational debt levels in dermatology trainees and effects on subsequent training choices: An update

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Educational debt levels of physicians in residency continue to rise and continue to outpace inflation. In previous work examining dermatology residency debt levels from 1999-2004, we did not find a relationship between debt levels and fellowship choices. The objective of this analysis is to examine whether career choices of graduating dermatology residents appear to be effected by debt, given the persistent continued increases in debt levels. Anonymous surveys were given to graduating dermatology residents who participated in the Galderma Board Review course from 2005-2012. Response rates ranged from 34% to 75%, with a mean rate of 48%. Average debt for dermatology trainees when they graduated residency during the eight year time period ranged from $95,567.57 to $178,153.9 with 47% to 76% of trainees reporting debt annually. From 2005-2012, debt level did not generally appear to be a significant factor overall in determining fellowship status or primary post-training practice setting. Notable exceptions occurred in 2007 in which fellows were significantly more likely to report a lack of debt than their non-fellowship trained counterparts (44% versus 34%, p<0.05). Also, in 2009 significantly more residents with debt were likely to enter private dermatology practices than were those without debt (60% versus 22%, p<0.05). Number of returned surveys lacked completed debt or primary post-training practice setting data. This survey and debt levels reported may also be limited by reporting bias. Debt levels for dermatology residents are high, have increased substantially over time, but continue to have little correspondence with the fellowship training choices of US dermatology residents.

1012

Immunogenicity of the anti-IL-17A antibody secukinumab in healthy subjects and patients

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Secukinumab (AIN457) is a new fully human monoclonal antibody (mAb) targeting IL-17A for treatment of inflammatory diseases. mAb administration can be associated with immunogenicity via induction of anti-drug antibodies (ADA), which can lead to loss of exposure, loss of efficacy due to altered pharmacokinetics (PK) and/or functional neutralization, and in the worst case, anaphylactic reaction and immune complex diseases. Our immunogenicity assessment followed a 3-tiered approach: 1) samples were analyzed for ADA in a screening assay that took a 5% false-positive rate into account; 2) positive samples were tested in a confirmatory assay (competition with excess drug) that identified true positive responses; 3) true positive samples were quasi-quantified via titration. While a Biacore-based assay was used during the early stages of the psoriasis and arthritis secukinumab program (up to Phase 2B), an MSD-based bridging immunoassay was applied during the later stages (Phase 3 and other indications). The MSD-based assay detects 4 ng/mL of positive control anti-secukinumab antibody and 500 ng/mL of this control in the presence of 14.7 µg/mL secukinumab, consistent with regulatory guidelines. Samples were obtained from subjects from 18 clinical studies in various indications during treatment and follow-up. In total 1582 subjects have been tested for ADAs, 486 with the MSD-based bridging immunoassay. Dosing regimens included single doses such as 25 mg s.c. in psoriasis pts and multiple 7x10 mg/kg IV doses in MS pts over a 6-month period. None of the subjects tested developed sustained ADAs. In total 4 subjects (3, Biacore; 1, MSD-based assay) met the definition of treatment-related, transient positive immunogenicity, showing low ADA titers. None of these had evidence of loss of efficacy, altered PK, or reported allergy/hypersensitivity/adverse events. Based on available data, secukinumab appears to carry a low risk of immunogenicity. More data from ongoing Phase 3 studies are required to strengthen this encouraging finding in larger patient populations.

1013

Anxiety reduction using hypnotic induction and self-guided imagery during dermatologic procedures

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In this randomized control trial, rapid induction hypnosis followed by deepening and self-guided imagery was effective in alleviating anxiety associated with dermatologic surgical procedures. Patients scheduled for procedures who volunteered signed an informed consent and were randomized to one of three groups: live induction, pre-recorded induction, or control. Identical hypnotic induction scripts were used for live and audio pre-recorded inductions. Zero to ten range subjective unit scales were used for patient expectancy, motivation, anxiety and pain. Hypnotizability was assessed postoperatively using the Hypnotic Induction Profile. At the completion of the study, 13 patients had been randomized to each group. The live induction and pre-recorded group patients were each instructed after hypnotic induction to go to a place they would rather be and enjoy the sights and sounds and other experiences of their choice there. Data analysis of this study revealed that by 20 minutes into the procedure there was a significant p = 0.033 reduction in anxiety with live induction compared with controls. Pre-recorded induction results were similar to that of the controls. Reduction in anxiety with live induction compared with pre-recorded induction was close to significant at p = 0.075. Pain was minimal in all three groups, as would be expected when local anesthetic is utilized. All 13 patients in the live induction group reported experiencing self-guided imagery compared with no patients in the control group, p < 0.0001. Eleven of the 13 patients in the pre-recorded group reported experiencing self-guided imagery compared with no patients in the control group, p < 0.0001. Differences in experiencing self-guided imagery were not significant when comparing the live induction group with the pre-recorded group. Other factors showed no significant differences between groups. Live induction followed by self guided imagery was significantly more effective at reducing anxiety compared with controls, while pre-recorded induction was similar to controls with respect to anxiety levels.

1014

Outcome of patients with follicular mycosis fungoides

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Folliculotropic mycosis fungoides (FMF) is a rare variant of cutaneous T cell lymphoma in which neoplastic T lymphocytes display tropism for follicular epithelium. The objectives were to evaluate the outcome of patients with FMF at our institution. The setting was the Department of Dermatology, Department of Hematology and Oncology and Department of Pathology and Laboratory Medicine, University of California, Los Angeles. Cases of FMF were selected from the institutional registry of the department of pathology, the institutional database of patients who received a billing code of Mycosis Fungoides (IDC-9 202.x) from 1/1/2000 to 12/31/2010 and from the personal registry of Dr. Pinter-Brown. 21 patients (10 male, 11 female) with a mean age of 51 years were included. At initial presentation, 18 patients were stage I, 1 was stage II, 0 were stage III and 1 was stage IV. Median follow-up time was 18 months. The most common sites of involvement were the head and neck (90%). Oral Bexarotene was the treatment of choice in the majority (67%) of patients. All of the subjects are currently alive with disease. In conclusion, patients with FMF at our institution have a good prognosis in the short term. Further observation will need to be done in order to determine if our patients with FMF have better outcomes than previously reported cohorts, and to assess if treatment with oral bexarotene significantly influences the outcome of these patients.

1015

Circulating TSLP associates with decreased wheezing in non-atopic children

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Mouse models of atopic march suggest that systemic, skin-derived Thymic Stromal Lymphopoietin (TSLP) mediates progression from eczema to asthma. We investigated whether circulating TSLP is associated with eczema, allergic sensitization, or recurrent wheezing in young children. We conducted a prospective analysis of the relationship of plasma levels of TSLP to allergic sensitization and recurrent wheezing in the birth cohort from the Urban Environment and Childhood Asthma (URECA) study. Plasma TSLP levels were measured at 1, 2, and 3 years of age and correlated clinical parameters in each of the three years. We detected TSLP in 33% of 236 children for whom plasma samples were available for all three years. Overall, no significant association was found between TSLP and eczema or allergic sensitization. However, children without aeroallergen sensitization and with detectable TSLP at one year were significantly less likely to have recurrent wheezing by 3 years compared with those without aeroallergen sensitization and no detectable TSLP levels. In our birth cohort, circulating TSLP was not found to be predictive of recurrent wheezing during the first three years of life. Instead, it was associated with protection against recurrent wheezing among non-aeroallergen sensitized children. These findings provide a novel distinction between the pathogenesis of atopic versus non-atopic recurrent wheezing.

1016

The depletion of epidermal Langerhans cells is the common pathogenesis to the nutrient deficient trophic skin disorders including pellagra and biotin deficiency

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Trophic skin disorders are dermatoses caused by specific nutrient deficiency, those include pellagra, biotin deficiency, acrodermatitis enteropathica, necrolytic migratory erythema and necrolytic acral erythema. Pellagra skin shows the vacuolization of keratinocyte in the spinous layer, which is shared by those trophic disorders. Lately, the depletion of Langerhans cells was noticed in necrolytic migratory erythema and zinc deficiency. Moreover, we reported the complete depletion of Langerhans cells in human pellagra patients and pellagra model mice. We further analyzed the alteration of various cells in the biotin deficient patient and model mice those were fed with a biotin eliminated diet. In addition, we analyzed the temporal change of dendritic cells at skin and intestine using two groups of pellagra model mice. One group was fed with a niacin elimination diet, another group was given niacin antagonist, 6-aminonicotinamide. Langerhans cells were significantly decreased in biotin deficient patient. The numbers of Langerhans cell in mice fed with a niacin elimination diet were reduced to approximately 20% of wild type mice in 8 weeks, and those were completely disappeared in 1 week after administration of 6-aminonicotinamide. CD11b as well as CD11c positive dendritic cells in jejunum were also significantly decreased in pellagra model mice, which might explain the other symptom of pellagra: diarrhea. These data suggest that the depletions of the organ specific dendritic cells at skin and jejunum are the common and primary mechanism of trophic skin disorders. The necrolysis of keratinocytes, which is the main characteristics in these diseases, should be the secondary events due to the disturbed function of dendritic cells.

1017

Primary localized cutaneous amyloidosis: Association with atopic dermatitis

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Primary localized cutaneous amyloidosis(PLCA) is a chronic pruritic dermatological disorder of unknown etiology. Genetic mutations in cases of familial PLCA have been mapped to the oncostatin-M receptor(OSMR) β, subunit of interleukin(IL)-31 receptor. IL-31 has been implicated in the pathogenesis of atopic dermatitis(AD). The objectives were to assess if AD is more prevalent in patients with PLCA compared to patients with other conditions attending the same dermatology clinic. Secondarily, to investigate if the prevalence of AD, severity of itch, morphology and locations of PLCA differ between familial and sporadic forms. Consecutive patients with the clinical diagnosis of PLCA visiting a dermatology clinic were evaluated by a single investigator. Data on demographics, family history, morphological types and locations of PLCA, and itch score were collected and they were screened for concomitant AD based on history and physical examination. The control population consisted of consecutive patients with diagnoses other than PLCA seen in the same clinic. A total of 44 patients with and 97 controls were evaluated. The prevalence of AD in patients with PLCA was significantly higher than in controls, at 75% and 39.2% respectively (OR=4.66, 95% CI=2.10 to 10.3, p<0.0005). The prevalence of AD in sporadic cases was significantly higher than familial cases, at 84.4% and 50% respectively (OR=5.4, 95% CI=1.23 to 23.7). Mean itch levels, morphological types and locations of PLCA did not differ between familial and sporadic cases. In conclusion, AD was associated with PLCA and the association was stronger with the sporadic compared to the familial cases.

1018

***In vivo* regulation of acneic sebum composition leading to a healthy sebum profile**

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Acne is an inflammatory dermatosis of the pilosebaceous unit in which sebum plays an important role. In addition to hyperseborrhea, sebum composition in acne patients is different than that of healthy individuals (HI). Acneic sebum is enriched in oxidised squalene and oleic acid and deficient in linoleic acid and sapienic acid. These modifications are probably responsible for both comedones and inflammatory lesions.The aim of this study was to demonstrate the possibility to modify the lipid composition of the sebum in an acneic group. Then, a clinical double-blind study versus placebo was performed. Two groups of twenty individuals with acne-prone skin (AP) and one group of ten individuals with healthy skin were included. A complex of active ingredients (bakuchiol, mannitol, Ginkgo biloba) or the placebo was applied on the face twice daily. A quantitative & qualitative measurement of the sebum lipids was performed at days 0 and 56 by chromatography (GC/MS). At day 0, AP individuals had a different lipid chromatographic profile than HI. They presented a lower rate of sapienic acid and linoleic acid and a higher rate of oleic acid. After 56 days of treatment, the chromatographic profile of AP individuals treated with the active complex was very similar to that of the HI. Indeed, compared to day 0, the rate of squalene and linoleic acid was increased by 17% and 23% respectively, while the rate of oleic acid was reduced by 7%. Moreover, the rate of sapienic acid was preserved compared with day 0, but increased by 10% in the placebo group. This study demonstrates the ability to restore the sebum composition in AP skin towards the normal pattern and, therefore, that we may limit comedogenicity, improve the barrier function and anti-microbial defense of the skin, leading to biological sebum properties similar to those of a HI.

1019

HPV in non-melanoma skin cancer/pre-cancer in HIV

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HPV and UV exposure are implicated as co-factors in non-melanoma skin carcinogenesis. We have performed a case/control study of HPV in pre-cancerous skin lesions- squamous cell carcinoma (SCC)-in situ (CIS), actinic keratoses (AKs) and penile pre-cancer (PCIS) as well as non-melanoma skin cancer (NMSC) - basal cell carcinoma (BCC), SCC and penile SCC in HIV +ve and HIV –ve patients. DNA was extracted from microdissected, formalin-fixed, paraffin-embedded tissue and typed for beta, genital and wart HPV by broad-spectrum, highly sensitive assays. 236 lesions have been analysed from 58 HIV+ve cases and 59 HIV-ve controls. HIV+ve group: 29/58 (50%) patients +ve for any HPV type, with genital types most prevalent, followed by beta and wart. Genital types detected in 21/29 (72%: 9 BCC, 2 SCC, 5 CIS, 5 AKs, 4 PCIS, 1 Penile SCC: HPV 6,11,16,31,33,40,44,45,52,56,68,70); beta types:18/29 (62%: 8 BCC, 2 SCC, 5 CIS, 6 AKs: HPV 5,8,9,12,14,15,19,20,23,24,25,36,38,75,80,92,96); wart types:6/29 (21%: 8 BCC, 2 CIS, 1 AK: HPV 1,2,40). HIV–ve group: 32/59 (54%) patients +ve for any HPV type. Genital types found in 15/32 (47%: 4 BCC, 5 SCC, 2 CIS, 4 PCIS, 1 Penile SCC: HPV 6,11,16,18,39,44,45,51,74); beta types:16/32 (50%: 8 BCC, 3 SCC, 2 CIS, 4 AKs, 1 PCIS: HPV 8,12,14,15,19,22,23,24,25,36,38,76,80,92,93,96); wart types:10/32 (31%: 3 BCC, 4 SCC, 2 AKs, 1 PCIS: HPV 1,2,3,4,27,29). Multiple HPV types identified in 9/29 (31%) HIV+ve & 7/32 (22%) HIV-ve individuals. HPV is highly prevalent in NMSC/pre-cancer of HIV+ve and -ve patients. Although isolated mainly from non-genital skin, genital types (including high-risk oncogenic type 16) are the most common type in the HIV+ve group. Beta-types (the most prevalent HPV type in NMSC) are less common in the HIV+ve group. Multiple types are more prevalent in the HIV+ve group, possibly reflecting differences in immune status. NMSC in HIV is associated with a different spectrum of HPV compared with immunocompetent individuals.

1020

Identification of biomarkers of clinical response to Minoxidil topical foam in men with androgenetic alopecia: A microarray approach

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Sixteen healthy men ages 18-49 with Hamilton-Norwood type IV-V thinning were included in the study. Ten subjects used 5% minoxidil topical foam (MTF) twice daily for 8 weeks and 6 used placebo. Scalp biopsies were taken from the leading edge of hair loss from the frontal and vertex scalp at visit 0 and again after 8 weeks of active drug/placebo. Stereotactic photographs were taken of subjects at visit 0 and at 8 weeks. Subjects with visible hair growth on global photographs were considered "responders." Differential gene expression in the scalp biopsy specimens was examined using microarray gene chip analysis. BAM array Bayesian Analysis of Variance (BAM) and Ingenuity Pathways Analysis was used for identifying differentially expressed genes in responders compared to non-responders. G-protein coupled receptor signaling was the top canonical pathway that was upregulated, whereas NOS signaling pathway was down regulated in responders compared to non-responders. SNORD116-22 and other non-coding RNAs were specifically upregulated in all responders as compared to the non-responder and placebo group. The role of non-coding RNAs in follicular physiology has not been well studied. Further evaluation of these potential bio-markers of clinical response to MTF is warranted. Supported by an Independent Investigator grant form Johnson & Johnson Consumer Companies, Inc.

1021

Increased periostin levels in patients with systemic sclerosis

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Background: Periostin is one of the matricellular proteins, a class of extracellular matrix (ECM)-related molecules defined by their ability to modulate cell–matrix interactions. Recent studies revealed that periostin serves as a regulator of wound healing, inflammation, and fibrosis. In this study, we determined periostin levels in association with clinical characteristics in patients with systemic sclerosis (SSc). Methods: Expression of periostin was examined in primary fibroblasts and the skin obtained from SSc patients using PCR, immunoblotting and immunohistochemistry. ECM production induced by periostin was also evaluated. Enzyme-linked immunosorbent assay was performed to determine serum periostin levels in association with clinical characteristics in 56 patients with SSc (diffuse cutaneous SSc; dSSc n=16, limited cutaneous SSc; lSSc n=40) and 66 healthy controls. Results: Periostin was strongly expressed in the affected dermis and primary fibroblasts obtained from SSc compared to healthy subjects. Periostin was co-localized in αSMA+ myofibroblasts and CD31+ endothelial cells in SSc skin. Further, periostin enhanced ECM production in primary fibroblasts. Serum periostin levels in dSSc were markedly elevated compared to those in lSSc and controls. Patients with lSSc had increased periostin levels compared with healthy subjects. In addition, significantly higher levels of periostin were observed in dSSc with disease duration <5 years compared with those with disease duration >5 years. Furthermore, the modified Rodnan total skin score (MRSS) was positively correlated with periostin levels in SSc patients. Serial analysis revealed the relevance of MRSS and periostin levels in some dSSc during their progress of the disease. Conclusion: An elevated periostin level in SSc patients was correlated with severity of skin sclerosis. Periostin may be a potential biomarker reflecting for disease severity in patients with SSc.

1022

Comparative study of high resolution multifrequency ultrasound of the plantar skin in patients with various types of hereditary palmoplantar keratoderma

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High variable-frequency ultrasound has been recognized as a highly discriminative imaging tool for a wide range of cutaneous disorders. However, it has so far not been utilized in the diagnosis of genodermatoses. In this study, we assessed the usefulness of ultrasound technology in the diagnosis of pachyonychia congenita (PC) patients, who typically present with plantar hyperkeratosis associated with severe pain, as compared to patients with other forms of palmoplantar keratoderma. The study included a total of 16 patients, 7 patients with PC, 5 patients with epidermolytic palmoplantar keratoderma (EPPK) and 4 patients with Mal de Meleda (MDM), who underwent ultrasound examination of the plantar skin with high resolution multifrequency ultrasound equipment. Ultrasound scans performed over the calluses and at the proximal and distal plantar foot on both sides in PC patients demonstrated hyperechoic dots and lines within the epidermis compatible with hyperkeratinization, engorged varicose veins in the dermis and an anechoic layer interposed between the epidermis and the dermis, corresponding to blister fluid below the calluses. In contrast to PC patients, patients with MDM and EPPK demonstrated no blisters. Thus, PC patients, as opposed to a group of patients with MDM and EPPK, display subepidermal blistering beneath their calluses. This finding may help in the diagnosis of PC and may provide an explanation for the unusually painful nature of PC-associated plantar hyperkeratosis.

1023

Not only strawberry but also Bowenoid, hyperkeratotic and featureless-vessel patterns should be recognized as global features on dermoscopy for actinic keratosis

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Objective of this study is to investigate global and local features on dermoscopy of actinic keratosis in Japanese and classify them into groups based upon global features and to know the relationship between dermoscopy and pathology. This study is observational and performed at a university hospital with dermoscopy outpatient clinic. Dermoscopy and pathology data from 35 Japanese patients with actinic keratosis were used. Main outcome measures are four dermoscopic global patterns including strawberry pattern, Bowenoid pattern, hyperkeratotic pattern and featureless-vessel pattern and local features including whitish small round structures, milky red areas, whitish network, globular or glomerular vessels, linear-irregular vessels and whitish scaly areas. 9 cases were classified as strawberry, 2 were Bowenoid, 13 were hyperkeratotic and 11 were featureless-vessel pattern. Whitish small round structures were observed in 82.8%, milky red areas in 94.2%, whitish network in 25.4%, globular or glomerular vessels in 68.4%, linear-irregular vessels in 31.6% and whitish scaly areas in 60%. Whitish small round structures corresponded to follicular structures, milky red areas to atrophic areas with inflammation, whitish network to acanthotic Bowenoid lesion, globular or glomerular vessels to dermal papillae in Bowenoid lesion, linear-irregular vessels to superficial vessels in atrophic lesion and whitish scaly areas to parakeratotic horny layer, respectively. Strawberry pattern, a combination of whitish small round structures and milky red areas was observed in 82.8% in at least some part, however only 25.7% demonstrated the global feature of strawberry pattern following the hyperkeratotic (37.1%) and featureless-vessel pattern (31.4%). Therefore, it would be important for a correct diagnosis of actinic keratosis to know other variations of global pattern on dermoscopy for actinic keratosis.

1024

Human keratinocyte proline-rich protein (*hKPRP*) is a novel keratinization-related protein whose deficiency may contribute to development of atopic dermatitis

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Atopic dermatitis (AD) is a common inflammatory skin disease caused by interaction of genetic and environmental factors. To discover uncharacterized genetic factors, we performed allelic copy number analysis at missense single-nucleotide polymorphisms (SNPs) on 26 genes with copy number variation, which are involved in inflammation and skin barrier. By analyzing DNA from 110 subjects with AD and 84 controls in the Japanese population, we discovered a significant association between AD and human keratinocyte proline-rich protein (*hKPRP*), an epidermal marker isolated from calcium-induced differentiating keratinocytes. The T/A (rs4329520) in exon 2 of *hKPRP* is non-synonymous SNP in a conserved region in the mammals, which causes an amino acid change from cysteine to serine. The analysis of alleic copy number indicated that *hKPRP* locus was diploid in most of the Japanese subjects, but the frequency of allele A in severe cases of AD were significantly low ($p = 0.021$) as compared with controls. We next examined gene expression of *hKPRP* by RT-PCR analysis in skin biopsies from the subjects with AD (N=5) and normal skin (N=8). The expression of *hKPRP* in AD skin was significantly decreased as compared with normal skin ($p = 0.0028$). Immunohistochemistry revealed that hKPRP protein expression was localized in the uppermost part of granular layer, which was significantly attenuated in epidermis of AD lesional skin. These data suggest that *hKPRP* is a novel keratinization-related protein whose deficiency may contribute to development of AD.

1025

Intrinsic atopic dermatitis (AD) shows similar Th2 and higher Th17 immune activation compared to extrinsic AD

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AD is classified as extrinsic and intrinsic, representing approximately 80% and 20% of adult patients, respectively. While sharing a similar clinical phenotype, only extrinsic AD is characterized by high serum IgE levels. Since most AD patients exhibit high IgE, an "allergic"/IgE-mediated disease pathogenesis was hypothesized. However, current models associate AD with T-cell activation, particularly Th2/Th22 polarization. To define if AD shares a common pathogenesis across its variants, we obtained lesional and non-lesional biopsies of 51 severe AD patients (42 extrinsic and 9 intrinsic AD, with similar mean disease activity/SCORAD among the groups), and analyzed the molecular and cellular skin pathology of intrinsic and extrinsic AD using gene-expression (RT-PCR) and immunohistochemistry. A significant correlation between IgE levels and the SCORAD ($r=0.76$, $p<10\text{-}5$) was found only in extrinsic AD. Marked infiltrates of T-cells and dendritic cells and corresponding epidermal alterations (K16, Mki67, S100A7/A8/A9) defined lesional skin of both variants. However, a higher activation of all inflammatory axes (including Th2) was detected in intrinsic AD, particularly significant for Th17 and Th22-cytokines. Positive correlations between Th17-related molecules and SCORAD were found only in the intrinsic phenotype, while only extrinsic AD showed positive correlations between SCORAD and Th2-cytokines (IL-4, IL-5), and negative correlations with differentiation products (loricrin, periplakin). Although a difference in Th17 activation exists between intrinsic and extrinsic AD, we identified common disease-defining features of T-cell activation, production of polarized cytokines and keratinocyte responses to immune products. Our data indicate that a Th2 bias is not the sole cause of high IgEs in extrinsic AD and suggest common T-cell mediated-disease mechanisms, with important implications for T-cell targeted therapies.

1026

Predictors of health related quality of life in psoriatic patients

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Nowadays it is marked that not only objective symptoms of the disease influence health related quality of life (HRQoL), but also personal resources (e.g. optimism) play a significant role in functioning with the chronic disease. The aim of the study was to investigate relations between HRQoL and medical and psychological variables. The goal was also to determine predictors of HRQoL. The study sample consisted of 60 psoriatic patients (30 females, 30 males; age range: 20-70 years; mean±SD 44.91±14.78). The range of disease duration was from 3 months to 54 years; mean±SD 18.76±13.50. Disease severity was estimated by PASI Score (Psoriasis Area and Severity Index) and ranged from 0.6 to 27.4 (mean±SD 9.32±5.97). Itch Severity Evaluation Questionnaire (Szepietowski, Reich, 2010) was used to evaluate itch. The methods to estimate optimism (Life Orientation Test - LOT-R; Scheier et al) and HRQoL in dermatological patients (SKINDEX-29, Chren et al) were used. The statistical significance was set at 0.05. Global itch, itch range and intensity correlated with worse physical functioning. Itch intensity influenced negatively also social functioning and global HRQoL. Optimism correlated with all subscales of HRQoL. The patients who manifested stronger optimism, presented better physical, emotional and social functioning, and global HRQoL. On the basis of performed regression analysis only optimism appeared to be a predictor of HRQoL (Beta = -0.40). The differences between females and males in HRQoL were observed. Women presented worse physical functioning and global HRQoL. The role of optimism in psoriatics is underlined and it is related to better HRQoL. The influence of optimism in determinig HRQoL appears to be more significant than objective symptoms of disease. It can be concluded that psychological interventions employment enhancing personal resources could be beneficial for psoriatics.

1027

Ustekinumab improved psoriasis without altering T cell immunity: Cytokine production, differentiation, and T cell receptor repertoire diversity

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Ustekinumab is a fully human IgG1κ monoclonal antibody targeting interleukin (IL)-12/23 p40 subunit. The pivotal role of IL-12/23-mediated pathway has been recognized in various inflammatory disorders especially in psoriasis. Recently the long-term efficacy and safety of ustekinumab for moderate-to-severe psoriasis patients was evaluated in phase 2/3 clinical trials, and the risk for serious adverse effects, infections, and malignancies was not significantly increased. Ustekinumab inhibits the produced IL-12/23 p40 subunit function, and therefore suppressive effects in interferon-γ production and immune systems are concerned. However, the effects on CD4+T cell function by ustekinumab have not been fully investigated. In this study, we analyzed changes in the cytokine production from memory CD4+ T cells and differentiation of naïve T cells into Th1, Th2, or Th17 cells in psoriasis patients treated with ustekinumab. We also analyzed the effect on T cell receptor repertoire diversity. The blocking of IL-12/IL-23p40 improved the skin manifestations without altering immunological profundity in Th1/Th17cells cytokine productivity. Furthermore, ustekinumab has limited effects in naïve T cell development, and T cell development milieu was maintained around normal levels. The staining with antibody to TCR BV subfamily showed all of the subfamilies were relatively reserved compared to normal volunteer, and no particular collapse in T cell receptor repertoire diversity was observed. As a result, ustekinumab improved clinical manifestation of psoriasis without interfering the cytokine productivity of memory T cells nor T cell maturation.

1028

A new sensitive scratch recorder for human dermatitis: Evaluation of nocturnal scratching sound of AD patients

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Quantitative analysis of itching in patients with atopic dermatitis is indispensable for the evaluation of the disease activities and responses to various therapies. However, the objective evaluation system for itching is very limited. We have developed a new objective scratching behavior detection system using a wristwatch type sound detector. The scratch sound detected on the wrist is acquired into PC through the filtering, squaring and smoothing process by specific hardware. Subsequently, the data was automatically processed and judged for the scratching movement using specific software based on the periodicity and the energy of signal. Twenty-four measurements for volunteers with healthy condition or atopic dermatitis are evaluated comparing a video record analysis system. Ratio of the scratching time in sleeping time evaluated with these two systems was almost identical. It takes only several minutes for evaluation of one night record. This scratch sound detection system is expected for a new objective evaluation system for the itching dermatitis and anti-itch therapies.

1029

5-Fluorouracil preconditioning followed by photodynamic therapy enhances apoptotic responses in squamous cell carcinoma through increased levels of p53

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Squamous cell carcinoma (SCC), arising from actinic dysplastic precursors, is a major problem in organ transplant recipients and in other patients with severe photodamage. Photodynamic therapy using aminolevulinic acid (ALA-PDT) works well for SCC in situ, but less well for deeper lesions . Recently we showed that preconditioning with methotrexate can enhance the responsiveness of SCC tumors to ALA-PDT, by enhancing heme pathway activity and protoporphyrin synthesis. Because 5-fluorouracil (5-FU) acts via the same pathway as methotrexate, we asked whether 5-FU might also enhance ALA-PDT in SCC tumors. Three experimental models were used: (i) murine SCC, generated by chemical carcinogenesis in hairless mice; (ii) subcutaneous A431 tumors (human SCC) in nude mice; (iii) actinic keratoses in human volunteers in a small clinical pilot trial. Topical or systemic 5-FU preconditioning for 3 days, followed by ALA, enhanced the accumulation of PpIX in tumors as measured by confocal microscopy of frozen sections (excitation 635 nm, emission > 690 nm). TUNEL assay done at 24 or 48 hr post-PDT showed persistent elevation of apoptosis in tumors preconditioned with 5-FU prior to PDT, relative to PDT treatment alone. Because 5-FU causes misincorporation of nucleotides into DNA and RNA, which can trigger a p53-mediated damage response, we tested the hypothesis that activation of p53 pathways might be a mechanism that contributes to enhanced PDT-mediated tumor death. Immunohistological evaluation of tumor sections revealed increased levels of wildtype p53, increased p21 and p27 (downstream targets of p53), and reduced levels of MDM2 (a negative regulator of p53). Persistent p53 levels were seen only in the 5-FU pretreated tumors, consistent with enhanced apoptotic responses to PDT. In conclusion, 5-FU in combination with PDT appears to provide additional benefits relative to either modality alone for the treatment of SCC, via a novel mechanism that involves activation of p53-mediated cell death pathways.

1030

Wound repair process comparison after the Er-Yag, CO2 and the 1064nm Q-switched Nd-yag lasers ablation: The basis of treatment of melanocytic nevus by the 1064 nm Q-switched Nd-yag laser

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Melanocytic nevus treatment is one of the most common procedures in dermatology. Most physicians currently use the CO2 or the Er-yag lasers to treat melanocytic nevus. But recently, there has been several articles which dealt with the treatment of melanocytic nevus by the 1064nm Q-switched Nd-yag laser (QSND). To compare the wound repair process and the tissue damage of the 3 laser types, the authors ir radiated the Er -yag, CO2 and the 1064nm QSND to the skin of a rat. The authors biopsied the subject rat on the first day, the fifth day and the tenth day after it was exposed to the laser. Each specimen was stained by H&E, Verhoff-van gieson & Masson-trichrome. It was ultimately determined that the rat skin which was irradiated with the 1064nm QSND showed the least amount of heat damage and was the quickest to repair from the tissue damage. Based on these results, we came to the conclusion that the 1064nm QSND with a photomechanical power that is capable of ablating epidermis and dermis can be a proper treatment modality for the removal of melanocytic nevus. When treating a patient with melancoytic nevus, physicians could consider the 1064nm QSND as a viable option.

1031

An investigational study to evaluate sildenafil for the treatment of lymphatic malformations

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Lymphatic malformations (LMs) are localized areas of abnormal development of the lymphatic system. Patients may present with pain, secondary infection, complications due to specific organ involvement, and death. Recently, we reported marked regression of LMs in three children after treatment with oral sildenafil. The objective of this investigational open-label study was to assess the efficacy of 20-weeks of oral sildenafil in reducing the volume and symptoms of children with LMs. Dosing for sildenafil was based on the European Medicines Agency guidelines as follows: if the subject weighed more than 20 kg, 20 mg was given three times a day (60 mg/day); if the subject weighed between 8 kg and 20 kg, 10 mg was given three times a day (30 mg/day). LM volume was calculated blindly using magnetic resonance imaging (MRI) that was performed before and after 20 weeks of sildenafil. Clinical response was assessed on weeks 0, 4, 12, and 20 and both the physician and parent evaluated the LM. We have complete data on 6 subjects (N=6; 3 boys, 3 girls; ages 13-79 months). LM locations included head/neck (N=5) and abdomen (N=1). Five subjects had a LM volume decrease (0.01-31.70%). One subject had a 4.0% volume increase; however, the subject had improvement in obstructive sleep apnea scores from 8.8 (moderate) with 26 episodes of apnea to 2.9 (mild) with 0 episodes of apnea. Subjects had a history of LM complications prior to sildenafil including infection (N=2), hemorrhage (N=1), and obstruction of anatomical structures (N=2). None of the subjects had these complications on sildenafil. Adverse events included nausea, rhinorrhea, mild insomnia, diarrhea, and fever. All LMs softened and became easily compressible. Several subjects requested to continue sildenafil after study completion because of the improvement they perceived. A national double-blind, placebo-controlled trial will be necessary to verify the beneficial effects of sildenafil on LMs.

1032

The pathogenic role of sweating disturbance in the development of lichen amyloidosis

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Lichen amyloidosis (LA) is characterized histologically by a deposition of amyloid in the papillary dermis. Although the deposition seems to be not the cause, the sequence of events leading to damage of keratinocytes and the subsequent deposition of amyloid remains to be elucidated. According to previous dermoscopic findings, the 'hub' corresponding to the center of the papule is surrounded by radial streaks, giving a volcanic crater-like appearance, suggesting involvement of sweat gland/duct-mediated inflammation. In this study, we asked whether sweating disturbance due to sweat duct blockage could represent an early event that triggers this skin condition. To this end, we quantitatively evaluated sweating responses to thermal stress in the involved and perilesional uninvolved areas in LA by using the impression mold technique, which we have recently established and allows an accurate quantification of sweat glands actively delivering sweat and their volume. A total of 4 patients with clinically diagnosed LA with preceding unsuccessful therapies for years were enrolled. In the 'hub', the complete absence of sweat droplets was observed while compensatory increases in sweat droplets were detected in the peripheral uninvolved areas. We have also observed similar, but less, sweating disturbance in lichen planus (LP) lesions not only in the lesion but also in the perilesional uninvolved areas. Compared with LP, the absence of sweat droplets in LA was more complete and was restricted to the 'hub'. Surprisingly, treatment with a moisturizer (heparinoid) under occlusion resulted in almost complete resolution by 2 weeks, at which time a sweat droplet appeared in the 'central hub'. The removal of amyloid by phagocytic cells associated with the clinical resolution was immunohistochemically confirmed. These findings indicate that LA is among a group of dermatoses that are caused by extravasated sweat, like other lichenoid diseases such as LP.

1033

Retrospective study of leukemia cutis demonstrates improved survival with stem cell transplantation

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Leukemia cutis, which refers to skin infiltration by lymphoid or myeloid malignant cells, is considered a poor prognostic factor in patients with hematologic malignancy. However, studies of the disease are limited, especially over the past decade despite major advancements in chemotherapeutics and stem cell transplantation. We performed a retrospective study of patients ≥ 18 years old diagnosed with leukemia cutis between 1/1/2000 and 10/1/2012 at Brigham and Women's Hospital/Dana Farber Cancer Institute. We identified 56 patients with leukemia cutis, of whom 51 suffered from acute myelogenous leukemia (AML). Three AML patients had aleukemic leukemia cutis (positive skin biopsy but negative blood and bone marrow samples for leukemic cells). Nine patients developed leukemia cutis despite leukopenic peripheral white blood cell counts. All but one patient had intermediate or adverse risk karyotypes. Patients ≤ 60 years old had longer average survival than those > 60 years old, although the difference was not statistically significant. There was however a significant increase in survival in patients that received stem cell transplantation compared to those that did not. Overall survival averaged 22 months for all AML patients with leukemia cutis, with a 1-year absolute survival rate of 36.1% and 5-year absolute survival rate of 24%, where all deaths were AML-related. This 5-year survival rate is comparable to the current national 5-year relative survival rate in adults with AML. This data suggest that i) leukemia cutis is possible despite absolute leukopenia, ii) stem cell transplantation may offer a survival advantage for leukemia cutis patients and iii) counter to previous thought, leukemia cutis may not adversely affect patient prognosis.

1034

Safety, pharmacokinetics and efficacy of AN2728 ointment, 2% in a phase 2 study of adolescents with mild-to-moderate atopic dermatitis

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Purpose: To evaluate the safety, tolerability and systemic exposure of AN2728 Topical Ointment, 2%, in subjects with atopic dermatitis (AD). Methods: Multicenter, phase 2, open-label study with a PK Phase (Days 1-9) and a Safety & Tolerability Phase (Days 10-28). 23 adolescents, ages 12 to 17 y, with mild-to-moderate AD involving 10-35% body surface area (BSA) were treated twice daily (BID) with AN2728 Ointment, 2% for 28 days, except on Days 1 and 8 when only an AM dose was applied. Plasma samples for PK analysis were collected on Days 1 and 8 pre-dose and at 1, 2, 4, 6, 8, and 24 h post-dosing as well as on Days 4 and 6 prior to AM dose. Global assessment of disease severity was based on the Investigator Static Global Assessment (ISGA), a 5-point scale from 0 (clear) to 4 (severe). Erythema, excoriation, exudation, lichenification, and pruritus were graded on a 4-point scale from 0 (none) to 3 (severe). Results: AN2728 Ointment, 2% was found to be generally safe and well-tolerated with the most common AE being application site reactions. No serious AE were observed. One subject discontinued due to AE (contact dermatitis). Plasma levels of AN2728 were low and dependent on BSA being treated. ISGA scores improved substantially over the 4-week treatment period. 35% of subjects achieved the treatment success criterion of "clear" or "almost clear" on the ISGA with ≥2-grade improvement from baseline. Substantial improvements in the primary signs and symptoms of AD, particularly pruritus, were observed. Conclusion: AN2728 is a boron-based phosphodiesterase-4 inhibitor, well-suited for the topical treatment of inflammatory skin disorders. Based on these Phase 2 results in adolescents with AD, AN2728 Ointment, 2% when applied BID for 4 weeks was generally safe and well-tolerated, provided low systemic exposure and produced substantial improvements in global disease severity as well as individual signs and symptoms of AD.

1035

Macrophages are critical for tumor formation in a xenograft model of CTCL

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Macrophages play key roles in tumor development and invasion in several human cancers, but little is known about their pathogenic role in cutaneous T cell lymphoma (CTCL), including mycosis fungoides (MF), the most common variant. We had previously shown that clodronate-containing liposomes could deplete murine skin macrophages and prevent T cell tumorigenesis in a murine model of CTCL. Herein, we used PCR Expression Arrays to profile the expression of inflammatory cytokines in tissue samples from 12 MF patients. Compared to normal skin controls, MF skin samples displayed increased mRNA levels of macrophage-related cytokines, including chemokine receptors CCR4, 5, 8, chemokines CCL1-5, CXCL9-11, IL10, IL1beta, and TNFalpha. Moreover, we detected immunostaining of CD163, a reliable marker of tumor-associated macrophages, in the tumor microenvironment of MF biopsy samples. To demonstrate that macrophages played a role in CTCL tumorigenesis, we xenografted human Hut78 CTCL tumor cells subcutaneously in NOD scid-IL2 receptor gamma chain-deficient mice (NSG) and compared tumor development after 30 days and depleted skin macrophages in one group of mice (n=5) with clodronate-containing liposomes. Mice treated with clodronate-containing liposomes show a marked decrease in tumor growth compared to a PBS-liposome-treated group (118 mm2 vs. 31 mm2, $p<0.001$). Immunostaining of clodronate-treated tissue revealed almost complete depletion of macrophages. We also noted a strong correlation between macrophage depletion and decreased expression of the vascular marker, CD31, and the lymphatic marker, podoplanin, suggesting a role for macrophages in angiogenesis. In vitro, clodronate-liposomes killed activated murine M2 macrophages, but not Hut78 cells, demonstrating selective ability to induce apoptosis in macrophages. Our data indicate that macrophages play a critical role in the progression of Hut78 cell tumor formation in skin, thus providing a new therapeutic strategy for CTCL.

1036

Photodynamic therapy serves two ends in the diagnosis and treatment of actinic keratosis with multiple lesions

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Actinic keratosis(AK) is a common premalignant skin condition which demarcation can be clinically problematic. Fluorescent images after topical methylaminolevulinate(MAL) has been used for the demarcation of AK. However, to our knowledge, validity of fluorescent images for the diagnosis of AK has never been studied. Photodynamic therapy(PDT) treats multiple AKs with excellent cosmetic results. MAL-PDT has proven to be clinically effective in AKs. The aim of this study is to evaluate the therapeutic efficacy of MAL-PDT for multiple AKs and to define the value of fluorescent images in evaluating the treatment response of AKs. Ten patients who have at least six actinic keratosis lesions in sun-exposed area were enrolled in this study. Before treatment, the number of lesions was evaluated by inspection. The lesions were treated with CO2 laser for superficial abrasion and subsequent topical MAL application for 3 hours. Fluorescent images were taken to measure the number of MAL-induced porphyrin fluorescence. Red light (LED arrays) was then illuminated with 37J/cm2. All patients were treated at 4 weeks, 16 weeks, and 20 weeks after initial treatment. We compared the number of AKs calculated by inspection and the fluorescence images. In all patients, total number of lesions was reduced both in inspection and fluorescent images. The number of AKs analyzed by fluorescent images showed a significant positive correlation with inspection. After four-session of treatment, eight patients (80%) showed treatment response of 75% or more. We concluded that MAL-PDT is an effective treatment especially for multiple AK lesions. Analysing the fluorescent images after topical MAL is a practical method for both diagnosis and evaluation of treatment response of AKs.

1037

Pathogenic cell types, molecular mechanisms and prognostic factors in EB virus-associated cutaneous T/NK lymphoproliferative disorders

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EB virus (EBV)-associated cutaneous T/NK lymphoproliferative disorders include classical hydroa vacciniforme (cHV), systemic HV (sHV), and hypersensitivity to mosquito bites (HMB). We have analyzed 1) pathogenic cell types, 2) EBV gene expression, and 3) molecular markers related to the prognosis. Eight of 9 (89%) patients with cHV or sHV showed increased numbers of EBV+ γδT cells (>5% of total lymphocytes), while 13 of 15 (86.7%) patients with HMB with or without HV-like eruptions were associated with EBV+ NK lymphocytosis (>32%). In addition to EBV+ cells, the skin infiltrates were composed of many reactive cytotoxic T lymphocytes (CTLs) in HV, and of both CTLs and NK cells in HMB. All 21 samples of circulating EBV+ lymphocytes revealed the latency infection pattern without any reactivation marker. In the skin lesions of sHV or HMB, however, 6 of 15 (40%) samples were positive for a reactivation marker, BZLF1 mRNA, while no BZLF1 mRNA was detected in all 16 cHV lesions. T/NK cell lines with latent EBV infection expressed BZLF1 mRNA after stimulation with PMA or TNF-α. These observations indicate that the EBV infection pattern changed from the latent infection to the lytic one in the severe cases, and that the lytic infection-associated EBV antigens might be targeted by the patients' immune responses. Statistical analysis of 46 patients demonstrated 3 risk factors: 1) disease types other than cHV, 2) onset age of over 9 years, and 3) BZLF1 mRNA expression. No prognostic correlation was observed in the proliferating lymphocyte subsets, anti-EBV antibody titers or EBV DNA load. HV is a disease of EBV+ γδT cells, while HMB is induced by EBV+ NK cells. Reactivation of EBV+ T/NK cells occurs in the skin, which in turn induces severe symptoms due to host immune responses, and is related to the poor prognosis.

1038

Systematic review of treatments for eczema informs clinical practice and highlights research gaps

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The aim of this overarching systematic review was to provide an up to date summary of the evidence for benefits and harms of treatments for eczema (syn. atopic eczema or atopic dermatitis). Six reference databases, including MEDLINE and the Cochrane Library, were searched from 2000 to 2011 using a highly sensitive search strategy. All randomized controlled trials in humans with eczema which compared two or more treatments; including placebo, vehicle or no treatment, and reporting at least one clinically relevant outcome were included. No language restrictions were imposed. The results of a Health Technology Assessment systematic review of treatments for eczema published in 2000 (283 trials) were synthesized with 236 new trials to create an updated review. The review covers antimicrobial and antiseptic agents, antifungal agents, non-pharmacological interventions, topical corticosteroids, calcineurin inhibitors, systematic treatments, complementary therapies, dietary interventions, phototherapy and other interventions which have been trialed for treating eczema. Good evidence of benefit to support the use of topical corticosteroids and calcineurin inhibitors was found, however, there was not enough evidence to make recommendations as to the most appropriate topical treatments and regimens. Reasonable evidence to recommend the use of educational interventions was also reported. There was enough evidence to suggest that probiotics, ion-exchange water softeners, and topical antimicrobials are not sufficiently effective to treat non infected eczema and to recommend that these treatments should not be used. This systematic and comprehensive overview of the trial evidence for eczema treatments can now be used to inform clinical guidelines and treatment pathways. It provides a clear and concise summary of the evidence and is in the public domain for the benefit of clinicians, researchers, systematic reviewers and policy makers to use in research and practice.

1039

Steroid treatment during the acute stage of severe drug eruptions is associated with improved long-term outcomes in the generation of autoantibodies: Longitudinal analysis up to 12 years of autoantibodies against epidermal proteins

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An understanding of the mechanisms by which autoimmune responses are generated and of how they might or might not lead to autoimmune diseases is of importance. Patients with severe drug eruptions, such as Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis(TEN) and drug-induced hypersensitivity syndrome (DiHS) are at greater risk of subsequently developing autoimmune diseases, because they are characterized by defective regulatory T cells. We therefore investigated how and when autoantibodies (Ab) could be generated in these patients. Sera obtained at various time points from these patients (28 DiHS, 30 SJS and 8 TEN) and 7 healthy controls were studied by indirect immunofluorescence (IIF) against rat bladder and immunoblotting against HaCat cell and recombinant periplakin. 54%, 32.6% and 53.6% of DiHS sera reacted with polypeptides of 250, 210 and 190kDa, respectively, which co-migrated with desmoplakin I, II and periplakin. 71% of DiHS sera reacted with any of them (plakins). SJS/TEN sera showed similar positive rates. The IIF staining pattern of the IgG deposits was cytoplasmic or nuclear. Immunoblotting with periplakin(1-324) demonstrated that DiHS sera, which contained autoAb to a 190kDa protein, reacted with this domain. These autoAb were detected throughout the observation period for maximum of 12 years regardless of prior epidermal damage, while in some patients the levels gradually increased with time. Surprisingly, all patients with DiHS not treated with steroids (n=16) developed autoAb to plakins, while only 33.3% of those treated with steroids (n=12) did so, indicating that immune responses preventable with steroids could trigger the generation of autoAb. Our results indicate that early resolution by steroids may lead to better long-term outcomes for patients at risk of subsequently developing autoimmune diseases.

1040

Safety and efficacy of a novel topical herbal-based lotion (KAM-0209) to manage psoriasis symptoms

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Psoriasis is a frequent, chronic, inflammatory skin disorder characterized by erythematous plaques covered with thick, silvery scales, often accompanied by intense pruritus. KAM-0209 cream is a bio-herbal treatment designed to exfoliate scaly skin and to calm irritation and redness in psoriasis patients. Active herbal extracts included in the product contribute to reduction of proinflammatory environment within the psoriatic lesions. In order to evaluate the effects of KAM-0209, Kamedis initiated an open-label, self-controlled, interventional study which included a cohort of 20 subjects with psoriasis. The purpose of the study was to assess the safety/efficacy of KAM-0209 cream in providing relief of psoriasis symptoms. Subjects were instructed to apply the body cream on affected areas twice daily for 6 weeks. Psoriasis Area and Severity Index (PASI, pruritus, the proportion of patients with at least 50% and 75% reduction in PASI (PASI50, PASI75 respectively) were measured at each visit (days 0, 14, 28 and 42). PASI steadily decreased throughout the study. Of the patients with mild to moderate psoriasis (PASI<15, N=12), 67% achieved PASI50 and 50% achieved PASI75 after 6 weeks. At the final visit, mean PASI decreased by 58% and mean pruritus (itching) decreased by 83% ($p < 0.001$) compared to baseline. Reduction of at least 50% in pruritus was reported by 10 out of 11 patients (92%). No worsening/adverse events were reported. Eighty five percent (85%) of subjects were satisfied with the treatment. Based on the results of this study, it was concluded that KAM-0209 is a safe and effective treatment for the relief of psoriatic symptoms, especially for mild-to-moderate cases of psoriasis. By providing a mechanical barrier, this treatment maintains a moist skin environment, protects the skin from additional irritation and facilitates the healing process. The addition of herbal extracts known for their anti-oxidant and photo-protective activities further protects the skin from oxidative stress, thus contributing to the restoration of the intact skin barrier.

1041

18-Fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) as a novel tool for quantification of psoriasis disease activity: Proof of concept from the Vascular Inflammation in Psoriasis (VIP) trial

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Psoriasis, like many skin diseases, lacks an objective biomarker. While several clinical measures of psoriasis disease activity exist, all remain clinician dependent and subjective in nature. As part of the VIP multicenter trial which was designed to study the effects of 12 weeks of adalimumab vs phototherapy vs placebo treatment on vascular inflammation as measured by FDG PET-CT, we also aim to examine the feasibility and utility of FDG PET-CT to objectively measure psoriasis activity in the skin. FDG PET is a powerful nuclear imaging technique that highlights metabolically active tissues labeled by preferential uptake of 18-FDG by high-glucose-utilizing cells such as cancer and inflammatory cells. The ability to identify inflamed tissues by FDG PET makes it a promising tool for imaging chronic inflammatory conditions such as psoriasis. In this proof of concept study of 4 subjects, we measured lesional skin metabolic activity by FDG PET-CT for the lower extremities at baseline prior to treatment. The mean metabolic volume product (MVPmean) was utilized as the measure of psoriasis disease activity. MVPmean is a product of the total volume of psoriatic plaques and mean standard uptake value (SUV) of all psoriatic lesions, and it represents a combined index of overall psoriasis extent and activity. MVPmean was highest (234.4 SUV-mL) in the subject with greatest clinical psoriasis activity and was lower (11.6, 21.9, 67.8 SUV-mL) in subjects with less clinical activity. These MVPmean values are similar to what is seen in patients with osteo- and rheumatoid arthritis. Our preliminary data suggest FDG PET-CT can be used to objectively quantify psoriasis skin activity and may be a powerful biomarker of psoriasis activity.

1042

Biomarkers elevated in atopic dermatitis (AD) are reduced by therapeutic blockade of IL-4 receptor α (IL-4Rα) signaling with REGN668/SAR231893 in patients with severe AD

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REGN668/SAR231893, a fully human monoclonal antibody against IL-4Rα chain that potently blocks both IL-4 and IL-13 signaling thus inhibiting the T-helper 2 (Th2) immune pathway, which is implicated as a key driver of atopic dermatitis (AD) pathogenesis. Analyses of serum levels of the Th2 markers thymus and activation regulated chemokine (TARC/CCL17) and total immunoglobulin E (IgE), as well as serum lactate dehydrogenase (LDH), all of which are associated with AD severity, were performed centrally on samples collected in a randomized, double-blind, placebo (PBO)-controlled trial (NCT01385657) of weekly subcutaneous doses of REGN668/SAR231893 (150mg and 300mg) or PBO for 4 weeks (last dose day 21, plus 8 weeks follow-up) in 37 adult patients with moderate-to-severe AD. A rapid reduction (median >70% from baseline) in TARC was observed in patients treated with 300mg REGN668/SAR231893 compared with PBO ($p<0.0001$), with suppression maintained for approximately 1 month after the last dose. The serum IgE median % change from baseline was significantly different from PBO as early as day 15 (300mg, $p=0.0379$), and continued to be significant through the end of the study (day 85), when it was -23.9% with 300mg REGN668/SAR231893 relative to a 41.7% increase with PBO ($p<0.0001$). REGN668/SAR231893 treatment was also associated with a statistically significant decrease from baseline in LDH (median reduction >12% at day 29 with 300mg REGN668/SAR231893 compared to a median 2.6% increase in the PBO group; $p=0.0051$). The most common adverse event was nasopharyngitis (n=9 [33%] vs. 2 [20%] for PBO). These results show that the IL-4Rα inhibitor REGN668/SAR231893 significantly suppressed serum biomarkers (TARC, IgE, LDH) associated with Th2 inflammation and/or disease activity in adult AD patients.

1043

Anti-nuclear antibodies and anti-ribonucleoprotein antibodies mirror cutaneous and systemic disease activity in discoid lupus erythematosus patients

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Background: In systemic lupus erythematosus (SLE), autoantibodies such as anti-dsDNA have demonstrated clinical utility in depicting and predicting disease activity. However, no similar studies to date have been performed for discoid lupus erythematosus (DLE). Identifying autoantibody biomarkers in DLE could help forecast disease progression, guide treatment, and lead to novel therapeutic targets. Objective: We sought to compare the association of autoantibodies against nuclear antigens with various disease activity markers in DLE patients. Methods: A cross-sectional study was conducted on 83 DLE patients in the University of Texas Southwestern Cutaneous Lupus Registry. ANA, dsDNA, ssDNA, RNP and additional ENA autoantibodies were measured on patient sera using ELISAs or multiplex-beaded array assays. Results were compared to various disease activity markers (e.g. complement levels, CLASI activity and damage scores, SLEDAI scores, number of ACR SLE criteria, number of oral lupus medications). Results: In all DLE patients, ANA and anti-RNP antibodies had significantly direct correlations with CLASI activity (r=0.31 (ANA), r=0.34 (anti-RNP)), SLEDAI scores (r=0.40 (ANA), r=0.31 (anti-RNP)), number of SLE criteria (r=0.59 (ANA), r=0.43 (anti-RNP)), and number of oral lupus medications (r=0.33 (ANA), r=0.30 (anti-RNP)). There were significantly indirect correlations with C3 (r=-0.52 (ANA), r=-0.57 (anti-RNP)), and C4 levels (r=-0.48 (ANA), r=-0.69 (anti-RNP)). Similarly significant trends were seen in DLE patients with positive ANAs. Conclusions: Based on their correlation with cutaneous and systemic disease activity markers and number of SLE criteria, ANAs and anti-RNP antibodies may contribute to progression from cutaneous to systemic disease in DLE patients. These circulating anti-RNP antibodies could represent important therapeutic targets to inhibit disease spread in DLE. Longitudinal studies need to be performed to assess prognostic potential of these antibodies in DLE patients.

1044

Early alteration of microRNA predicts response to extracorporeal photopheresis in cutaneous t-cell lymphoma

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Extracorporeal photopheresis (ECP) is an effective therapy for the cutaneous T-cell lymphomas, mycosis fungoides (MF) and Sézary syndrome (SS), but there are those for whom ECP has no benefit. Additionally, it can take up to 9 months to appreciate a therapeutic clinical response to ECP. MicroRNA (miRNA) are non-coding RNA that are often altered in cancer, including MF/SS. We hypothesized miRNA would be altered early in ECP treatment and would predict clinical response. Thirteen patients with MF/SS receiving monotherapy ECP were retrospectively identified. RNA was extracted from peripheral blood mononuclear cells from pre- and 3 months post-ECP. Quantitative RT-PCR was performed to evaluate miRNA levels. In those with sustained clinical response (CR) between 6 to 12 months, levels of specific miRNA increased 3 fold at 3 months post-ECP, whereas non-responders (NR) had a 0.24-fold reduction ($p=0.045$). Indeed, an absolute increase in the miRNA at 3 months was significantly associated with a clinical response ($p=0.022$). There was no difference in expression levels of other miRNA between CR and NR. Notably, a lower baseline level of one miRNA pre-ECP was associated with clinical response at 1 year. Our data indicate that in MF/SS, miRNA levels are altered early in ECP, and increasing levels of specific miRNA predicted clinical response. Our data also reveal that lower initial levels of a miRNA was associated with clinical response. We propose that early changes in miRNA and/or baseline levels can help augment therapeutic decision-making. However, larger studies are warranted to further evaluate the role of miRNA as predictors of response to ECP in MF/SS.

1045

Vismodegib as an adjuvant to surgery for basal cell carcinomas

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Aberrant Hedgehog (HH) signaling pathway is responsible for basal cell carcinoma (BCC) development. Vismodegib, an oral HH-pathway inhibitor, is FDA approved for the treatment of advanced/metastatic BCCs and is taken indefinitely. Our goal was to determine the safety and efficacy of 3 months minimum of vismodegib as adjuvant treatment prior to Mohs surgery for operable BCCs. Our primary endpoint was the reduction in surgical defect size after vismodegib. We enrolled 10 subjects with BCCs of any subtype in an open label, single arm, interventional trial of vismodegib 150mg daily. This study was powered to determine a 30% reduction in surgical defect size. We report the interim analysis on the first 5 patients with a total of 7 BCCs treated for 3.4 months (SD: 0.9). Mean size of baseline tumors were 3 cm2 (range: 1 to 6.6 cm2) and occurred primarily on the face (6/7 tumors). All subjects experienced mild side effects (Grade 1) of taste loss, muscle cramps and hair loss. Vismodegib was stopped early in 1 subject due to Grade 2 elevation of liver enzymes. Vismodegib reduced the mean size of the Mohs surgical defect by -1.1cm2 (95%CI: -0.19 to- 2.0, P=0.026) or -38% from baseline expected lesion size with 2 mm margins (presumptive 1 stage Mohs resection). Vismodegib also reduced tumor area by -1.4cm2 (95%CI: -0.19 to-2.0, P=0.008) or -46% from baseline. All patients who completed at least 3 months of therapy required only 1 Mohs stage for excision. Further sectioning of Mohs specimens, revealed no evidence of BCC in 3/7 tumors after therapy, and equivocal diagnoses in 4 cases as these resembled infundibular cysts staining positive for BerEp4 and BCL2. No tumors recurred over a median follow-up of 3 months (range: 2-6 mo), but longer follow-up is needed. In conclusion, vismodegib appears to reduce BCCs prior to surgical excision thereby reducing the surgical defect. However, future challenges include the interpretation of histology for residual BCC after vismodegib and the presence of miniaturized hair follicles that may confound tumor margin clearance.

1046

Soluble DC-HIL protein is a novel and useful blood marker for melanoma

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We discovered that the cell surface receptor DC-HIL expressed by melanoma cells is a potent inhibitor of T cell activation. We also discovered that B16 melanoma cells, implanted subcutaneously into mice, shed a soluble form of DC-HIL into peripheral blood that can inhibit T cell function in a manner similar to the surface receptor. Additionally, the amount of circulating soluble DC-HIL protein (sDC-HIL) increases proportionally with the volume of subcutaneous B16 tumor. Prompted by these findings, we posited that growth and metastasis of melanoma in humans may also be marked by increasing blood levels of sDC-HIL. We addressed this hypothesis by collecting blood from patients diagnosed with melanoma spanning the entire spectrum of clinical staging. Patients' sera (2.5 µl) were enriched for sDC-HIL using WGA lectin-beads, applied to SDS-PAGE, and immunoblotted with our 3D5 anti-DC-HIL mAb. Blood concentration was calculated by comparing intensities of 3D5-stained bands to those of recombinant DC-HIL applied to the same gel. This system allowed reliable detection of sDC-HIL as low as 0.1 ng/ml of serum. Healthy controls (n=10) and patients with dysplastic nevi who were otherwise healthy (n=3) displayed almost identical near-baseline sDC-HIL levels (0.3 ± 0.2 and 0.3 ± 0.1 ng/ml, respectively). By contrast, melanoma patients exhibited significantly higher levels by Student's t test ($p>0.05$): 3 ± 2 ng/ml for stage 0 (n=9); 0.5 ± 0.2 for stage I (n=3); 6 ± 5.1 for stage II (n=5); 19 ± 14 for stage III (n=6); and 20 ± 13 for stage IV (n=9). sDC-HIL blood level rose progressively with cancer stage, except for stage I (which was underrepresented by relatively fewer patients assessed). Our results indicate sDC-HIL to be a novel and potentially useful blood marker for melanoma, even for cases confined to skin (stages 0, I, II). The issue of whether differences in blood sDC-HIL can discriminate (prognosticate) between aggressive vs. non-aggressive tumors is the subject of our ongoing studies.

1047

Bone marrow transplantation has better outcomes than umbilical cord blood transplantation in recessive dystrophic epidermolysis bullosa (RDEB)

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RDEB results from deficiency of type VII collagen (C7), which results in lack of attachment between the epidermis and dermis, severe blistering, and a poor quality of life. Between 2007 and 2012, 18 individuals (0.7-20y) with life-threatening, severe generalized RDEB have undergone allogeneic hematopoietic cell transplantation at the University of Minnesota. Of these, 13 were treated with a myeloablative (MA) conditioning (busulfan, fludarabine [FLU], and cyclophosphamide [CY]) and 5 were treated with non-MA conditioning (CY, FLU, anti-thymocyte globulin, and total body irradiation). RDEB individuals were transplanted with bone marrow (BM) from an HLA-matched sibling (n=10), an HLA-matched unrelated donor (n=3), or a partially matched umbilical cord blood (UCB, n=5). Importantly, non-MA conditioning was well tolerated with a marked reduction in risk of infection and pulmonary or renal toxicity. For the entire cohort thus far, the overall probability of survival is 73% (95% CI, 49-96%) with 11 demonstrating partial to marked biochemical and clinical improvement in mucocutaneous disease on the basis of C7 expression, body surface area affected, and resistance to blistering. We conclude that BM is the preferred graft (alive and engrafted: 11 of 13 [85%]) versus UCB (1 of 5 [20%]) (p-value = 0.02) and that early results with the non-MA conditioning are promising in terms of toxicity profile and engraftment. Overall, HCT has the potential of being a durable, systemic therapy for many people with different forms and severities of EB, and sets the stage for using BM cells in the treatment of a broad spectrum of extracellular matrix disorders.

1048

Blocking IL-4Rα signaling with REGN668/SAR231893 rapidly suppresses major pathogenic pathways in severe atopic dermatitis

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Atopic dermatitis (AD) is the most common inflammatory skin disease. Existing therapies are limited, creating a large unmet medical need. Since the Th2 cytokines IL-4/IL-13 play a key role in AD, inhibition of these cytokines may provide an effective treatment. REGN668/SAR231893, a fully human monoclonal antibody against IL-4Rα chain, potently blocks IL-4/IL-13 signaling. We evaluated the effects of IL-4Rα blockade on the molecular skin pathology in patients with severe AD treated with REGN668/SAR231893 or placebo (PBO). Pre- and post-treatment lesional skin biopsies were obtained from 18 consenting patients who participated in randomized, double-blind, placebo-controlled trials of 4 subcutaneous weekly injections of 75, 150, 300mg REGN668/SAR231893 or PBO. Significant dose-dependent changes from baseline gene expression were detected by RT-PCR and microarrays at week 4. Improvements of 52% and 25% in an established AD transcriptome (defining the gene expression differences between lesional and non-lesional AD phenotypes) were observed in the 300mg and 150mg doses respectively, paralleling significant decreases in the respective EASI scores, versus a 25% worsening in the PBO group. 894 probes were significantly modulated in the higher-dose group (fold change>2, $p<0.05$). Significant decreases in the mRNA expression of genes related to hyperplasia (K16, MKi67), T- and dendritic cells (Granzyme B, CD1b, CD1c) and potent inhibition of Th2-associated chemokines (CCL17, CCL18, CCL22, and CCL26) were noted without significant modulation of Th1-associated IFNγ, IL-17 and IL-22. This is the first report of a targeted biologic therapy in AD showing clinical and molecular disease suppression, achieved after only 4 weeks of IL-4Rα blockade. These data suggest IL-4/IL-13 as the major pathogenic cytokines in AD that drive a complex Th2-centered inflammatory axis in this disease.

1049

Systemic treatment of patients with severe atopic dermatitis (AD) with an anti IL-4Rα mAb (REGN668/SAR231893) results in rapid and sustained improvements in disease signs and symptoms

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REGN668/SAR231893, a fully human monoclonal antibody (mAb) against IL-4Rα chain, potently blocks IL-4 and IL-13 signaling. The mAb was evaluated in 3 randomized, double-blind, placebo (PBO)-controlled Phase 1 trials: one in healthy volunteers (HV, N=48, single escalating IV or SC doses), and 2 in adults with AD (combined N=67, 4 weekly SC doses of 75, 150, 300mg or PBO on days 1, 7, 14 & 21, with 85 day follow-up). REGN668/SAR231893 was well-tolerated with an adverse event (AE) rate similar to PBO and no identified dose-limiting toxicities or serious AEs. The most common treatment emergent AE was nasopharyngitis. In the HV study, REGN668/SAR231893 significantly reduced serum Thymus and Activation Regulated Chemokine (TARC/CCL17) and IgE, confirming mechanism of action, and reduction was even more pronounced in patients with AD ($p<0.0001$ vs PBO). Patients enrolled had severe AD, with mean affected BSA of 48.8%, EASI score of 28.3, SCORAD of 63.3 and NRS pruritus score (0-10) of 6.0. REGN668/SAR231893 reduced pruritus and improved skin disease in a dose-dependent fashion within 7 days after initial dose. Proportion of patients who achieved an EASI50 response at day 29 was 71.4% in the 300mg arm vs 18.8% for PBO ($p=0.0025$), and NRS pruritus score decreased by 45.4% vs 18.6% for PBO ($p=0.0016$). The effect was sustained through day 85 for EASI50 and day 75 for NRS pruritus. The mAb significantly improved other clinical outcomes vs PBO at day 29: mean % change IGA ($p=0.0002$), EASI ($p<0.0001$), BSA ($p=0.0037$), and 5D pruritus ($p<0.0001$). Improvements were generally observed by Day 8 and persisted after end of treatment. The favorable safety profile, reduction in TARC/CCL17 biomarkers and rapid, marked, and sustained clinical improvements in adult patients with severe AD strongly support further evaluation of REGN668/SAR231893 for the treatment of AD.

1050

IL-4Rα mAb REGN668/SAR231893 for the treatment of severe atopic dermatitis itch

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Chronic itch is the hallmark of atopic dermatitis (AD) and impacts QoL for millions of patients (pts). Few studies have assessed itch as a major end point in AD trials. REGN668/SAR231893, a fully human monoclonal antibody (mAb) against IL-4Rα chain, potently blocks IL-4 and IL-13 signaling. In a phase 1b study (NCT01385657), pts with severe AD were given 150 or 300mg REGN668/SAR231893 or placebo (PBO) SC weekly for 4 wks. The mAb was well tolerated. The most common adverse event was nasopharyngitis (n=9 [33%] vs 2 [20%] for PBO). Pruritus was measured using a twice-daily Numeric Rating Scale (NRS; 0-10) to generate an average weekly NRS score and a bi-weekly 5D Pruritus Scale; both were exploratory objectives. The 5-question 5D scale assesses multiple dimensions of itch: degree, duration, direction, disability, distribution. Mean baseline NRS and 5D scores were 5.5 and 19, respectively. Average weekly NRS scores rapidly decreased (mean % change from baseline, vs PBO) by 31.9% at wk 2 ($p<0.02$), 55.2% at wk 7 ($p=0.01$) in the 300mg group vs +1.3% and -17.3% respectively in the PBO group. Rapid reduction in 5D scores was observed in pts treated with 300mg REGN668/SAR231893 (mean % change -28.2% at day 15, $p=0.0009$; -37.1% at day 29, $p=0.0007$; -42.5% at day 43, $p=0.012$; +3.6%, +8.1%, -9.4% respectively in the PBO group). Serum levels of CCL17, a marker of IL-4/IL-13 activity, rapidly declined on treatment. Both CCL17 and pruritus were suppressed for several wks following end of treatment. The 5D score significantly correlated with CCL17 ($r=0.46$, $p=0.004$ at baseline; $r=0.55$, $p=0.002$ at day 29) and EASI scores in this study ($r=0.41$, $p=0.011$ at baseline; 0.62, $p<0.0001$ at day 29). The rapid, sustained improvement in pruritus seen in adult pts with AD treated with REGN668/SAR231893 suggests IL-4/IL-13 signaling is a key mechanism for AD pruritus. Correlation between pruritus and CCL17 levels highlights the relationship between IL-4/IL-13 mediated inflammation, disease activity, and pruritus in severe AD.

1051

Isolated facial vasculopathy responding to pentoxifylline

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Isolated facial vasculopathy is a rarely diagnosed entity, reported previously only in the context of systemic lupus erythematosus (SLE) and with the use of levamisole or cocaine adulterated with levamisole. It has a predilection for involvement of the cheeks and ears. Treatment, largely based on case reports, involves withdrawal of the offending drug and occasionally systemic corticosteroids. Herein, we report a novel case of an otherwise-healthy 65-year-old woman with isolated facial vasculopathy responding to pentoxifylline alone. The patient presented with multiple 3-7mm nonblanching purpuric papules over her cheeks against a background of erythematous, edematous and confluent plaques. The purpuric lesions progressed to involve her nose and bilateral helices. Biopsy demonstrated vasculopathy with involvement of both superficial and deep vessels. There was extensive acute and organizing fibrin thrombus formation, but no evidence of vasculitis. Her laboratories were notable for an ANA of 1:640 speckled and ESR of 25. Extensive hypercoagulable, vasculitis, and autoimmune work-ups were otherwise unremarkable. She had no history of cocaine or other drug use. On the basis of these findings, the patient was diagnosed with facial vasculopathy and treated with pentoxifylline 400mg orally twice daily and demonstrated a rapid response. To our knowledge, isolated facial vasculopathy in the absence of SLE or levamisole has not been previously reported. In addition, this patient responded successfully to pentoxifylline alone, making this a novel report for this therapeutic intervention. Pentoxifylline reduces blood viscosity and improves flow by promoting leukocyte and erythrocyte deformability and blocking neutrophil activation and adhesion. Based on this patient's rapid response and pentoxifylline's favorable side-effect profile, we propose that pentoxifylline be considered in cases of isolated facial vasculopathy.

1052

Treatment of actinic cheilitis with topical photodynamic therapy

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Since actinic cheilitis is considered as premalignant, proper treatment is important to prevent transformation into squamous cell carcinoma. To date, invasive treatment modalities such as surgical resection and carbon dioxide laser ablation have been reported as a usual treatment option. However, actinic cheilitis is located in the cosmetically important area, cosmetic outcomes need to be considered. Because photodynamic therapy (PDT) showed high efficacy and good cosmetic results in the treatment of actinic keratoses, we tried to treat actinic cheilitis with topical PDT using methyl aminolevulinate. A total of ten cases of actinic cheilitis diagnosed by skin biopsy were enrolled in this study. For assessment of treatment efficacy, the histopathologic confirmations with rebiopsy as well as clinical assessment were performed by three investigators. When a residual lesion was observed clinically or histologically, the additional PDT was performed. Except two cases that showed complete response, most lesions of actinic cheilitis were not completely removed by PDT despite of multiple treatment. The reason for the low therapeutic efficacy is not clear, but there may be several explanations. Rapid regeneration of mucosal epithelium compared to the skin may result in a lower efficacy of PDT. Inadequate uptake of photosensitizer due to dilution through saliva is also possible explanation of poor therapeutic outcome. In this context, intralesional injection of photosensitizer may enhance the cure rate of PDT. In conclusion, we suggest that topical PDT may not be suitable for treatment actinic cheilitis.

1053

A role for VEGF in prurigo? Blood level and expression in the skin is increased and correlates with vascular remodelling and disease activity

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Vascular endothelial growth factor (VEGF) is known as the major skin angiogenesis factor and can be produced by various resident skin cells including keratinocytes. We have recently shown that anti-VEGF treatment dramatically improved clinical symptoms in a patient with prurigo. Here, we aimed to identify and characterize the role of VEGF in the pathogenesis of prurigo. To this end, we assessed VEGF levels in the serum and VEGF and VEGF-receptor 2 (VEGFR2) immunoreactivity (IR) in the skin of prurigo patients (PP). VEGF levels were found to be significantly higher in PP as compared to healthy controls (191.9±38.5 pg/ml vs. 48.7±8.4 pg/ml, $p<0.001$) and VEGF staining revealed a strong increase in IR in the epidermis, dermis and subcutis of PP, while VEGFR2 IR was comparable to healthy controls. To identify consequences of increased VEGF expression in the skin, we next analyzed the number and size of vessels in the skin of PP and healthy controls. PP exhibited a marked increase in the number but not the size of blood vessels in PP as compared to controls as assessed by staining of the endothelial cell marker CD31 (13.5 ± 0.2 vs. 5.6 ± 0.6, per microscopic field, $p<0.05$). This increase in small blood vessels correlated closely with the epidermal thickness in prurigo lesions ($r2= 0.86$, $p<0.0001$). The number of lymph vessels was assessed by quantitative immunohistochemistry using D2-40 staining and was found to be similar in PP and healthy controls. As we have found that VEGF levels in PP correlate well with disease activity ($r=0.525$, $p<0.005$), we speculate that the observed profound vascular remodelling in PP might contribute to the pathogenesis of prurigo and that targeting of VEGF in PP might present a novel therapeutic strategy.

1054

Racial/ethnic disparities in the prevalence, severity and health outcomes of childhood atopic dermatitis

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Atopic dermatitis/eczema (AD) is a chronic inflammatory disorder of skin which may cause significant sleep disturbances and impair quality of life. Previous studies found differences in the morphology and distribution of AD lesions in different races/ethnicities. However, little is known about the racial/ethnic disparities of the epidemiology of AD. We used the 2007 National Survey of Children's Health, a prospective US population-based questionnaire study of 91,642 children age 0-17 years. We investigated the disparities of AD prevalence, severity, sleep impairment and overall health in African-American/Black (AAB) and Hispanic children and assessed their access to healthcare. Multivariate survey logistic regression models were constructed that controlled for age, sex, race/ethnicity (AAB, non-Hispanic, or Hispanic compared with White, non-Hispanic). Overall, AAB children had a significantly higher prevalence of AD (logistic regression, adjusted odds ratio [95% confidence interval]: 1.60 [1.45–1.77], $P<0.0001$), whereas Hispanic children had a lower prevalence of AD (0.72 [0.63–0.81], $P<0.0001$). AAB children with AD also had more severe disease (1.83 [1.35–2.48], $P=0.0001$) and were more likely to have ≥2 nights/week of impaired sleep (1.35 [1.04–1.74], $P=0.02$). Both AAB (0.81 [0.67–0.99], $P=0.04$) and Hispanic (0.73 [0.56–0.96], $P=0.02$) children with AD were less likely to report their overall health as being excellent. Both AAB and Hispanic children with AD were more likely to be currently uninsured (AAB: 3.27 [1.60–6.66], $P=0.001$, Hispanic: 3.79 [2.03–7.10], $P<0.0001$) or have public insurance such as Medicaid (AAB: 6.71 [5.12–8.80], $P<0.0001$, Hispanic: 4.60 [3.18–6.65], $P<0.0001$). In conclusion, there are significant disparities in the prevalence, severity, sleep impairment, overall health and access to care in AAB and Hispanic compared with White, non-Hispanic children with AD.

1055

Relationship of TNFalpha and p40 genes promoter polymorphisms with the efficacy to anti TNFalpha therapy

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The objective was to study the effect of polymorphisms in TNF-α and p-40 genes on the response to the treatment with antiTNF-α agents in patients with moderate-to-severe psoriasis. Single nucleotide polymorphisms (SNPs) in TNFα-238 (G>A), TNFα-308 (G>A), TNFα-857 (C>T), TNFα-1031 (T>C), IL12 (T>G and G>C) and IL23 (C>T and G>A) were genotyped in 104 patients. We studied the association of these SNPs with the efficacy at three and six months (PASI50, PASI75, PASI90, % improvement of PASI, % improvement BSA) in 133 treatments with antiTNFα agents (32 infliximab, 60 etanercept and 40 adalimumab) Patients with TNFα-238GG genotype reached more frequently PASI50 and PASI75, and the improvement of PASI and BSA was higher at six months than those with TNFα-238GA genotype ($p=0.03$, $p=0.041$, $p=0.005$, $p=0.000$). Patients with TNFα-857CT/TT genotype showed higher improvement of PASI at 6 months ($p=0.052$) than patients with CC genotype. Those patients who had TNFα-1031TT genotype showed a better improvement of PASI at 3 months ($p=0.014$) and 6 months ($p=0.003$) and, a higher frequency of these ones reached PASI50 at 3 and 6 months ($p=0.002$, $p=0.026$) than those with a TNFα-1031TC genotype. Patients with IL23-GG genotype achieved PASI50, PASI75 and PASI90 at three months ($p=0.004$, $p=0.1$, $p=0.061$), and PASI75 and PASI90 at six months ($p=0.062$, $p=0.013$) more frequently than those with a GA genotype than patients with GA genotype. In our study we have found a relationship between some TNFα and p40 polymorphisms and the response to antiTNFα drugs.

1056

Reflectance confocal microscopy for the monitoring of actinic keratoses undergoing photodynamic therapy

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A pilot clinical study was designed to evaluate the feasibility and longitudinal reproducibility of in vivo confocal reflectance microscopy(RCM) imaging for the assessment of AKs, and to identify predictive RCM structures of clinical response in the setting of photodynamic therapy (PDT). Seven patients undergoing PDT using a Metvix® protocol for the treatment of actinic keratoses were recruited between Nov-Dec 2012. Each study subject underwent RCM imaging of 2 actinic keratoses and an area of photodamaged skin at baseline, after Metvix® incubation time, after red light exposure (peak wavelength 630nm, 37J/cm2), and at 1 week follow-up time. Following a standardized imaging acquisition protocol, image blocks were obtained from the stratum corneum (SC), the mid epidermis (ME), dermo-epidermal junction (DEJ), and papillary dermis from all study lesions and time points. Images were analyzed according to several established RCM features. A preliminary assessment indicates that accurate and reproducible RCM imaging over 4 time points could be performed in 95% of Grade-1and 84% of Grade 2 AKs. Following Metvix® application and preceding the exposure to red light increased refractility at the level of the SC and ME was observed in 6/7 subjects, as well as 1+ inflammatory response (IR) at the level of DEJ in 5/7 subjects. Following the exposure to red light and 1 week after the intervention a 2+ IR was observed in 6/7 and 5/7 subjects respectively. Presence of dendritic cells was observed in 2/7 subjects immediately after red light exposure and after 1week follow-up time. A preliminary assessment of this pilot study indicates that monitoring of AKs undergoing PDT is feasible and that an IR can be observed early on in the process. Ultimately, correlation between RCM findings and clinical outcomes will be necessary to validate the utility of this imaging modality in the objective monitoring of AKs.

1057

Itch and pain are prognostic markers for depth of invasion and inflammatory cell constitution in nonmelanoma skin cancer: Results of a large clinicopathological study

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While skin cancers are exceedingly common, little data exist correlating frequently encountered dermatologic symptoms, including itch and pain, with histopathological features. This prospective, clinicopathological study enrolled 268 patients representing 339 histopathologically confirmed biopsies of cutaneous neoplasms including 166 basal cell carcinomas (BCC), 146 squamous cell carcinomas (SCC), and 27 melanomas. Patients presenting to the dermatologic surgery clinic for excision of their skin tumors filled out questionnaires including validated scales assessing itch and pain intensity of their tumors. Investigator blinded histopathological examination assessed depth of invasion, ulceration, and intensity/type of inflammation. Statistical analysis employed a multiple logistic regression model controlling for age, sex, chronic pain or itch related conditions, multiple skin tumors, and transplant status. The prevalence of itch and pain across all skin cancers was 36.9% and 28.2%, respectively. However, these symptoms were mostly absent in melanomas. Pain intensity was significantly associated with depth of invasion, ulceration, degree of inflammation, neutrophilic infiltrate, and presence of eosinophils (p=0.0012, 0.0022, 0.0022, 0.0018, 0.0059). Itch intensity was significantly associated with degree of inflammation, neutrophilic infiltrate, and presence of eosinophils (p=0.0001, 0.0403, 0.0167). These findings provide support for the notion that itch often emanates from the upper layers of the skin while pain is associated with deeper processes. This study also demonstrates that a simple bedside assessment of itch and pain is a valuable prognostic marker for histological characteristics and can aid clinicians in tailoring management and treatment aggressiveness.

1058

Phase II trial of Brentuximab vedotin (SGN-35) for CD30+ cutaneous T-cell lymphomas and lymphoproliferative disorders

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Brentuximab vedotin (SGN-35), a CD30 monoclonal antibody (cAC10) conjugated to microtubule disrupting agent, monomethyl auristatin E (MMAE), targets the CD30 surface receptor. Safety and efficacy of SGN-35 was evaluated in a Phase II open-label trial conducted in CD30+ lymphoproliferative disorders (lymphomatoid papulosis (LyP) or primary cutaneous pc-ALCL) or CD30+ mycosis fungoides (MF) +/- large cell transformation. SGN-35 dosing was 1.8 mg/kg for 30 min every 21 days for up to 16 doses. Response assessment required > 2 doses and a 50% decrease in active LyP number, pc-ALCL tumor measurement, or modified skin weighted assessment tool (MF). Twenty-one F and 25 M with median age of 59.5 years (range 31-86 years) were evaluable. Overall responses were seen in 31/46 (67.3%) with CR of 32% (15/46). LyP (n=9) and pc-ALCL (n=3) had 100% CR rates. Twenty-seven MF patients had ORR of 44% which varied based on low (<10%), medium (10-50%) or high (>50%) expression of CD30. Median duration of response (DOR) for LyP and pc-ALCL was 22 weeks (range 9-38). mDOR for MF was 12 wks (range 6-48). Adverse events (related, any grade) were neuropathy (59%), drug rash (27%), diarrhea (22%), fatigue (30%), alopecia (14%), myalgias and nausea (18%). Grade 3-4 events were neutropenia (n=3), nausea (n=2), chest pain (n=2), deep vein thrombosis (n=1), transaminitis (n=1) and dehydration (n=1). Dose reductions to 1.2 mg/kg were for grade 2 neuropathy (n=15), and transaminitis, arthralgias, and fatigue (n=1 each). Withdrawals were for neuropathy (n=2), drug rash (n=3), lack of efficacy (n=1), and infusion reaction (n=1). In conclusion, this phase II clinical trial demonstrates that Brentuximab vedotin is an effective, safe targeted therapy for CD30+ CTCLs - MF, pc-ALCL, and LyP with high overall response rate of 67.3%, including100% in LyP/pc-ALCL, and 44% in CD30+ patch/plaque MF regardless of CD30 expression.

1059

Possible predictors of treatment-failure and detailed dynamics of autoantibodies and markers of systemic inflammation in psoriasis patients under treatment with Adalimumab and Etanercept

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TNF-α inhibitors Adalimumab(ADA) and Etanercept(ETA) are used to treat psoriasis and psoriasis-arthritis. Predictors for treatment failure and detailed data on dynamics of autoantibodies and markers of systemic inflammation are lacking. We present a retrospective data analysis of 113 patients with psoriasis receiving ADA and 64 psoriasis patients receiving ETA. Anti-nuclear antibody (ANA) titres, anti-doublestranded-DNA (anti-dsDNA) concentrations, leucocyte counts, neutrophile counts, and C-reactive protein (CRP) concentrations at baseline and during treatment were recovered. Treatment failure (TF) encompassing loss-of-response and serious adverse events was chosen as clinical endpoint. Median ANA-titres and anti-dsDNA concentrations increased significantly under treatment with ADA. Neutrophile counts significantly decreased while counts of leucocytes other than neutrophils slightly but significantly increased under treatment with both biologics. Baseline values, dynamics, concomitant treatment, and biographical parameters were examined to identify possible predictors of TF. Cox-regression analysis revealed a significant predictive effect for TF for baseline anti-dsDNA concentrations and neutrophile dynamics for ADA, and number of previous systemic treatments for both biologics. This study is suggestive for a role of autoantibodies and neutrophile dynamics in identification of psoriasis patients at higher risk of treatment failure under treatment with ADA.

1060

Pruritus, photosensitivity, and physical and social health impact health-related quality-of-life in patients with cutaneous dermatomyositis

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Cutaneous dermatomyositis (CDM) is a chronic condition that has a major impact on quality of life (QOL). We pilot-tested a novel QOL measure in individuals with CDM. The measure was based on a ranking task for 10 domains of health followed by stated preferences using a willingness-to-pay quality of life (WTPQoL) instrument. The 10 domains included pruritus, photosensitivity, social comfort, emotional health, functionality, sleep, concentration, intimacy, physical comfort, and self-care. We interviewed 9 participants in-person using the scripted WTPQoL tool, and asked each to rank the domains in order of level of impact by CDM. We then asked participants whether they would be willing to pay out-of-pocket for a hypothetical cure for each domain, and if so, the US dollar amount. Monetary values were interpreted as relative, rather than absolute. Physical comfort, pruritus, and photosensitivity were the most frequently highly ranked domains, ranked highly by 88.9%, 77.8%, and 77.8% of participants respectively. Median amounts participants were willing-to-pay were highest for a hypothetical cure for photosensitivity ($100,000, 25th quartile (Q1) = $80,000, 75th quartile (Q3) = $20,000,000), pruritus ($100,000, Q1 = $5,000, Q3 = $5,000,000), and social comfort ($100,000, Q1 = $5,000, Q3 = $5,000,000). Median amounts were also high for emotional health ($80,000, Q1 = $5,000, Q3 = $5,000,000), functionality ($80,000, Q1 = $5,000, Q3 = $5,000,000), and physical comfort ($50,000, Q1 = $5,000, Q3 = $5,000,000). In this study, we successfully pilot-tested a ranking task and WTP stated preferences for health-related QOL across 10 CDM-relevant domains. We found that participants placed the greatest weight on physical comfort, pruritus, and photosensitivity as impacting health-related QOL, and were willing to pay the most for a hypothetical cure for photosensitivity, pruritus, and social comfort associated with CDM.

1061

Microneedle pretreatment may reduce incubation time in photodynamic therapy

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Microneedle (MN) devices hold potential for revolutionizing dermatologic practice yet are underutilized. We tested the effect of MN pretreatment on complete response rate (CRR) of actinic keratoses (AKs) when used in photodynamic therapy (PDT) with topical 5-aminolevulinic acid (ALA) and blue light (417 nm). We report preliminary data from a pilot, prospective, computer randomized, single-blind, controlled, split-face, rater-blind, clinical trial. Treatment arm was pretreated with MN to one side of the forehead followed by 20, 40 or 60 minutes ALA incubation. Randomly assigned contralateral forehead was treated with sham MN pretreatment followed by 60 minutes ALA incubation (control). Subjects' faces were cleaned with alcohol prior to MN application. We used arrays of solid, polymer, 650nm MNs. Primary outcome was CRR (lesion count reduction normalized to pretreatment lesion count) after one treatment at the one month follow up. Secondary outcomes were: post MN treatment and post PDT treatment pain measured by visual analogue scale (VAS, 0-100mm) and adverse event rate. Average CRR (SEM) for the 20, 40 and 60 minutes treatment and control arms were 77% (8.8) & 69%(2.8); 80% (5.3) & 86% (4.0); and 69% (11.7) & 79% (5.1) respectively (N=8, p=0.35; N=8, p=0.29; N=6, p=0.28). Average pain scores after MN pretreatment (SEM) in the treatment and control arms were 11.2 (2.8) & 1.7 (0.6) mm respectively (N=28, p<0.01). Average pain scores after PDT light treatment (SEM) in the 20, 40 and 60 minutes treatment and control arms were 16.8 (8.2) & 20.3(8.4); 15.8 (9.4) & 18.7(8.2); and 34.2(9.8) & 26.3(8.1) mm respectively (N=8, p=0.34; N=9, p=1.0; N=11, p=0.21). No adverse events reported. This study models translation of basic science knowledge on MN into clinical practice. MN pretreatment was tolerated well and our interim data suggests no significant difference in PDT efficacy using abbreviated incubation times with MNs versus traditional 60 minute incubation without MNs.

1062

Sticky Platelets Syndrome (SPS). A frequent cause of primary thrombophilia

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In 1986 Mammen et al described a group of patients with thrombosis in different organs both arterial and venous who had abnormal adhesive patterns under the influence of epinephrine and ADP. SPS is a dominant autosomic rather frequent condition but poorly known. In some settings even its existence is denied. Here we show a small series of 14 cases of SPS detected by platelet agregometry. Five of the 14 patients had skin manifestations: Atrophy blanche (2),severe livedo reticularis (1), Idiopathic Raynaud (1), Erythema nodoso / livedoid vasculopathy (1). Five patients without skin manifestations had internal pathology such as pulmonary embolism (1) bilateral deep vein thrombosis of the legs (2), another one arterial mesenteric thrombosis and pulmonary thromboembolism, thrombosis of the cerebral longitudinal sinuses (1) and the last one premature delivery with placental thrombosis. In recent years it has been established that in primary thrombophilia it is usual that exist more than one abnormality. In this series three patients had the SPS as only abnormality. The other shared the presence or de abnormal gene (677) for the methylentetrahydrofolate reductase (5), prothrombin mutation 20210 (2), Plasminogen activator/inhibitor) (1) and in one case antiphospholipid antibodies. Thus primary thrombophilia should be kept in mind in all areas of the medical care.

1063

Early ablative carbon dioxide fractional laser for acne scars in asian patients undergoing oral isotretinoin

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Acne scar is associated with substantial reductions in quality of life, so treatment should be initiated as early as possible. Recently, it is shown that laser treatment at the time of the procedure significantly improves the appearance and texture of scars. The objective of this study is to evaluate the evolution of healing from ablative fractional CO2 laser of depressed scars resulting from acne conducted within during and/or 1 to 3 months after oral isotretinoin treatment. This was an interventional, retrospective study involving 20 patients with depressed facial scars. An ablative fractional CO2 laser was applied to the entire face. Ablative fractional CO2 laser was performed to areas of scarring. A 6-month to 4-year reepithelization follow-up was conducted. All of the patients presented with normal reepithelization, and neither hypertrophic scars nor keloids were observed. Depressed acne scar revision was satisfactory. Our observations may contribute to the discussion of the negative influence of oral isotretinoin on wound healing. Other studies are necessary to reevaluate the current recommendation of a 6- to 12-month waiting period after oral isotretinoin treatment before performing ablative fractional laser for acne scar.

1064

Reversible suppression of normal thymic output in patients with leukemic cutaneous T cell lymphoma

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Patients with leukemic cutaneous T cell lymphoma (L-CTCL) have a number of unexplained immune abnormalities, including widespread neutrophil activation, marked losses of circulating T cell diversity by spectratyping and compensatory proliferation of surviving T cells. We now report that patients with L-CTCL also have reduced circulating naïve T cells. Although the number of naïve T cells in healthy individuals decreases gradually with age, a significant number of naïve T cells are present in the blood of older individuals and are thought to arise from both continued thymic output and from an increased lifespan of naïve T cells in older individuals. The absolute numbers/ml of benign naïve T cells (CD4+CD45RA+CD45RO-) was significantly decreased in patients with L-CTCL (systemic CTCL) as compared to healthy controls whereas the number of naïve T cells in patients with MF (localized CTCL) did not differ from healthy controls. In healthy individuals and MF patients, numbers of naïve T cells declined gradually with age, but naïve T cells in patients with L-CTCL were markedly reduced regardless of age. Loss of naïve T cells occurred uniformly in L-CTCL patients regardless of whether the total white count was low, normal or elevated. CD31, a marker of recent thymic emigrants, was decreased on the few remaining naïve T cells in L-CTCL patients, suggesting ongoing decreased thymic output. Successful treatment of L-CTCL patients, regardless of modality, was associated with increased T cell receptor excision circles (TREC) and restoration of circulating naïve T cells, most of which were CD31+ and thus represented recent thymic emigrants. Our results suggest thymic output of naïve T cells is suppressed in L-CTCL, perhaps contributing to the immune deficits observed in these patients. However, this suppression is reversible and thymic output and naïve T cell counts recover following successful therapy.

1065

Treatment with methotrexate does not affect microvascular endothelial function in patients with psoriasis

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Psoriasis is associated with an increased risk of cardiovascular disease (CVD), possibly due to chronic low-grade systemic inflammation. Systemic anti-inflammatory treatment might reduce the risk of CVD. Our aim was to investigate if short term treatment with methotrexate influences microvascular endothelial function (MEF), an early surrogate marker of atherosclerosis, in patients with psoriasis. We prospectively studied a hospital cohort of patients with psoriasis (n=32). Measurements of MEF were performed with the Endo-PAT2000© device at baseline and after 8-10 weeks of treatment with methotrexate. At the same time points, we recorded anamnestic information, measured body mass index (BMI), waist- and hip circumferences, and blood pressure, and drew blood samples. Psoriasis severity was evaluated by Psoriasis Area and Severity Index (PASI) and the Dermatology Life Quality Index (DLQI). At inclusion, median patient age was 46 (range 18-82) years, and 50% were men. Median duration of psoriasis was 15 (range 2-67) years. The prevalences of patients diagnosed with hypertension, diabetes and hyperlipidaemia were 15.6%, 21.9%, and 12.5%, respectively. Median levels of cholesterols and HbA1c were all within the normal range, whereas Hs-CRP was slightly elevated (2.50 (0.10-58.00) mg/L.) Twenty-seven patients completed the study. After 8-10 weeks, median PASI had decreased significantly by 6.2 (from 9.8 to 3.6), and DLQI had decreased by 7 (from 9 to 2). No significant changes were observed in MEF, expressed by reactive hyperaemia index and augmentation index. Also, we saw no significant changes of BMI, waist-hip-ratio, blood pressure, and blood samples. In conclusion, short term treatment with methotrexate did not affect MEF in patients with psoriasis, suggesting that assessment of MEF does not add independent information for prediction of CVD in these subjects.

1066

Surface cathelicidin expression is a predictor of treatment success in papulopustular rosacea

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Over 16 million people suffer from rosacea in the US with few treatment options available. Numerous pathogenic factors are associated with papulopustular rosacea, but the molecular mechanisms remain unclear. Aberrant expression of particular biomarkers has been implicated in atopic dermatitis, psoriasis, and rosacea, playing a role in inflammation. A unique formulation of doxycycline (Oracea®, doxycycline 30 mg immediate release, doxycycline 10 mg delayed release beads) has already demonstrated equivalent efficacy with fewer adverse events compared with doxycycline 100 mg QD. This multicenter, randomized, double-blind, placebo controlled study evaluated Oracea® efficacy, safety, and its impact on inflammatory biomarkers in patients with papulopustular rosacea. The biomarkers evaluated included MMP9, KLK5, cathelicidin, and total proteases. Adults with papulopustular rosacea (N=170) who were treated daily with Oracea® capsules or a placebo capsule for 12 weeks were evaluated at baseline, and at weeks 2, 4, 8, and 12. At week 12 there was a significant decrease in the mean percent change in lesion counts for the treatment group compared to placebo (-44.6 and -25.2% respectively, P=.018). The mean lesion count also decreased more in the treatment group compared to the placebo group (-4.3 and -3.2, respectively). Tape strip samples of facial skin for both groups were obtained to assess biomarker levels at baseline and at each time point. Of the 4 biomarkers evaluated, logistic regression showed statistical significance for the cathelicidin as a predictor of clinical success (P=.029) and total protease activity as a predictor of Oracea® use (P=.047). Most adverse events were mild in both groups (62.2% and 64.0%). Two serious adverse events, chest pain and spontaneous abortion, were reported in the active treatment group, but were not related to the study medication.

1067

Quantitative evaluation of efficacy of photodynamic therapy for port-wine stains using erythema index image analysis

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Background: Methods for quantitatively evaluate the efficacy of photodynamic therapy (PDT) for port-wine stains (PWS) are still needed for clinical practice and studies. Methods: 50 pairs of pictures before and after PDT of 40 PWS patients were selected. Each PWS lesion was labeled with a marker of red color graded 0—9. These pictures were taken without assistance of instruments to keep same position or distance and were referred to as 'experimental' images. 70 labels were photographed at a fixed position and distance with the assistance of a bracket and the images obtained were referred to as 'standardized' ones. An independent group of three experts viewed the photos and assessed the efficacy. The images were processed and measured for erythema index (EI) with the ImageJ freeware. The EI difference (deltaEI) and the percent change of deltaEI (ratioDeltaEI(%)) of the labels and the PWS lesions was computed separately. Results: Significant differences of EI, deltaEI and ratioDeltaEI(%) were found between each two grades of the color markers in both standardized and experimental images. DeltaEI of lesions achieved 'almost cured' and 'great improvement' after PDT was significantly reduced than before PDT. Significantly greater percentages of lesions were assessed as 'response' and 'significant response' in those of beforeDeltaEI ≥ 35 compared to those of beforeDeltaEI < 35. The ratioDeltaEI(%) decrease of lesions assessed as 'almost cured', 'great improvement' and 'some improvement' was significantly reduced sequentially. Conclusion: The EI image analysis is a valid method for quantitatively evaluating efficacy of PDT for PWS.

1068

The use of hemoglobin saturation ratio as a means of measuring tissue perfusion in the development of heel pressure sores

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The heel is a common site of pressure wounds. The amount of pressure and time needed to develop these wounds is dependent on various factors including pressure surface, patient s anatomy, and co-morbidities. We studied the use of the hemoglobin saturation ratio as a means of assessing heel perfusion in various pressure settings. The mixed perfusion ratio in the heels of five volunteers was assessed on three pressure surfaces and at off-load as a baseline. The surfaces studied were stretcher pad, plastic backboard without padding, and pressure reduction gel. Each surface was measured for five minutes with a real time reading. On the stretcher, the average StO2% decrease was 26.2± 10 (range 18-43). The average StO2% decrease on the backboard was 22.8 ± 12.3 (range 8-37), and 24.0 ± 4.8 (range 19-30) on the gel pad. The StO2% drop had a leveling off with stretcher, and gel pad but with backboard had a continued slow drop at 5 minutes. This study demonstrates that hemoglobin oxygenation ratio can be used to assess a tissue's direct perfusion in the setting of tissue pressure and can also be used to better assess the affects of pressure reduction surfaces. Using this method, a comparison of surfaces reveal a continued drop with a hard surface and plateau with all other surfaces. A comparison of gel versus stretcher shows a comparable reduction in tissue perfusion and therefore a similar pressure and shear reduction effect. While oxygenation ratios can be used to assess pressure precautions in skin care, further studies will be needed to determine time to skin breakdown as they pertain to pressure and tissue oxygenation.

1069

Genetic factors influencing anti-epidermal growth factor receptor (EGFR) antibody toxicity to the skin

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The majority (75-91%) of patients undergoing metastatic colorectal cancer and treated with anti-EGFR monoclonal antibodies develop a papulo-pustular skin rash. Over 75% of skin rashes are severe, sometimes requiring treatment discontinuation. Certain polymorphisms within the EGFR gene may be associated with an increased risk of skin toxicity. Our study aims (i) to identify EGFR polymorphisms associated with increased incidence or greater intensity of papulo-pustular rash in the Basque population, and (ii) to explore a putative association between EGFR polymorphisms and tumor response to EGFR inhibitor-mediated treatment. To this end, we conducted an observational longitudinal study with both retrospective and prospective inclusion of 45 Basque patients undergoing metastatic colon cancer and treated with EGFR inhibitors cetuximab and panitumumab. The EGFR gene polymorphisms analyzed included CA-SSR, EGFR-R521K, 216 G/T exon 21 and 191 C/A exon 19. Relevant clinical variables in patients' history have also been collected. The results are currently being analyzed. We expect to find an association between EGFR polymorphisms and the severity of the rash and/or tumor response.

1070

Recurring nearly deadly mosquito bites in a patient with mast cell activation syndrome

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Background: Mosquito allergy is an entity that causes severe large or atypical vesicular and even necrotic local allergic reactions at bite sites in some individuals. Systemic reactions including urticaria, angioedema, dyspnea, or hypotension are less common. Objective: We report a unique case of mast cell activation syndrome and recurring grade IV allergic reactions to mosquito bites. Methods: To confirm the mosquito allergy we performed skin prick testing with whole-body extract of two mosquito species that are common in middle Europe (Culex pipiens and Aedes communis). Further, CD63 up-regulation in basophils as a measure of basophil activation was determined by flow cytometry after stimulating patient's and control's basophils with whole-body extract of both mosquito species. To show that specific IgE in patient's serum mediated the severe allergic reactions we looked for specific IgE against mosquito via CAP. Results: Skin prick test with histamine as a positive control showed a wheal of 5 mm at the maximum diameter and a flare. Prick test with Culex pipiens gave a positive result with a wheal of 7 mm. Aedes communis skin testing showed a small papule of 2 mm. The negative control did not produce any reaction. The skin prick test was negative in all four healthy controls for both mosquito species. The patient's basophil activation with CD63 up-regulation to Culex pipiens extract was 90%. This was clearly elevated compared to the highest basophil response of a healthy control (38%). 62% of the patient's basophils were activated by the Aedes communis. The highest response of the basophils of a healthy control to Aedes communis extract was 24%. Specific IgE against mosquito was not detected by CAP. The total IgE was normal with 48.4 kU/l (<100 kU/l). Conclusion: We confirmed the patient's mosquito allergy by prick test and flow cytometry and thus identified the first case worldwide with a grade IV allergic reaction to mosquito.

1071

Complexity of skin ulcers: Pyoderma gangrenosum and lymphoma dominate in a university hospital in China

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All inpatients with skin ulcer as the predominant manifestation at the Dermatology Department of Peking University Third Hospital during the past 5 years were reviewed. The various causes, therapeutic options, and clinical responses were analyzed. Of 23 patients with skin ulcers, there were 11 males and 12 females. The average age was 50.09 ± 21.02 years with range 12 to 83 years. Five patients were diagnosed as pyoderma gangrenosum (1 case combined with myelodysplastic syndrome, 1 case with rheumatoid arthritis, the others without relevant concomitant disease). Five patients were diagnosed as lymphoma (3 cases combined with fungal infection). The other diagnoses were Behcet's disease, stasis dermatitis, nasal mucormycosis with leukopenia and anemia, scrofuloderma with lymph node tuberculosis, hidradenitis suppurativa, artificial ulcer, trauma with diabetes, burn with diabetes, and eosinophilic cellulitis, 1 or 2 cases of each etiology. Among the 5 patients with pyoderma gangrenosum, 4 was cured by steroids (equivalent dose of methyl prednisolone 24mg to 120mg) and/or immunosuppressive agents combined with traditional Chinese medicine (1 case with micro-skin autograft), but 1 case responded poorly despite significant pain release initially. The patients of lymphoma with fungal infections were given systemic antifungal therapy, ulcers showed different degrees of improvement. Two patients with ulcer caused by physical factors and diabetes were treated only with traditional Chinese medicine (intravenous salvia and wet compress of Kangfuxin/Lithospermum oil) and responded well. The diseases causing skin ulcers are various, which should make careful differentiation. Pyoderma gangrenosum could be very recalcitrant. Lymphoma combined with fungal infection is common. Traditional Chinese medicine may be beneficial for the patients.

1072

Identification of a targetable CTLA4-CD28 gene fusion in Sézary syndrome

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Sézary syndrome (SS) is a rare and aggressive form of cutaneous T cell lymphoma (CTCL) involving blood and skin. Treatment options remain limited in the advanced stage of disease. We describe a 68-year-old female patient with advanced SS, history of resistance to multiple systemic therapies and no remaining effective treatment options. In order to identify possible therapeutically targetable molecular changes, we sequenced the genome and transcriptome from two metastatic tumors using germline DNA (saliva) and unmatched normal, cultured T cell RNA as controls, respectively. Copy number analysis of DNA sequence data implied copy gains in at least 1437 genes and losses in 1115 genes. Among the somatic events uncovered was a highly amplified intrachromosomal structural rearrangement involving the CTLA4 and CD28 loci. This event created a novel fusion between the extracellular domain-encoding portion of T cell inhibitory receptor gene CTLA4 and the intracellular signaling domain-encoding portion of a highly related T cell activating receptor gene, CD28. Transcriptome data, as well as validation using targeted Sanger sequencing, confirmed the in-frame fusion transcript, which was expressed at high levels. This fusion is predicted to yield a novel stimulatory molecule on the tumor cell surface, potentially targetable by the anti-CTLA4 antibody drug ipilimumab. Treatment with ipilimumab resulted in a marked clinical response, with rapid resolution of skin tumors and erythroderma. These results illustrate the power of next generation sequencing and its potential to identify functionally relevant and immediately targetable aberrations of significant clinical relevance.

1073

Prevalence of eosinophils in drug eruptions

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An elevated number of eosinophils in skin biopsies has been traditionally considered as supportive of a diagnosis of cutaneous drug eruption. Provocative data have recently challenged this notion, suggesting that tissue eosinophilia is neither sensitive nor specific enough for the pathological diagnosis of cutaneous drug eruptions. These studies defined the existence of a drug reaction in small numbers of patients based on clinical criteria only, complicating their interpretation. To determine the diagnostic significance of tissue eosinophilia in cutaneous drug eruptions, we made use of a unique database established over the past decade at our institution which contains laboratory, histopathological and long-term follow-up data on a large series of cases referred because of suspected drug reaction. Our study population included 169 patients referred because of a skin eruption suspected of being due to a drug reaction. A patient was considered as having developed a true drug reaction based upon (1) compatible clinical findings, (2) a positive interferon-releasing assay, and (3) long term follow up data (including confirmation of the diagnosis through personal patient interview between 6 months and three years after initial ascertainment). On the basis of this set of stringent criteria, 67 patients (40%) were considered to have developed a true drug reaction Skin biopsies were obtained from all patients. We compared the number of eosinophils per high power field in patients with and without drug reaction using the Wilcoxon rank sum test with continuity correction. The number of eosinophils per high power field was significantly higher in patients without a true drug reaction than in patients with a true drug reaction (mean 6.54 versus 4.35 and median of 2 versus 1, respectively; $p<0.0001$). In conclusion, the present data collected through assessment of a unique cohort surprisingly demonstrate that the presence of eosinophils in skin infiltrate is not a reliable indicator of drug reaction.

1074

Effect of weight loss on the severity of psoriasis: A randomised controlled trial

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Psoriasis is associated with overweight and uncontrolled data suggest that the severity of psoriasis improves with weight loss. We performed a randomised controlled trial investigating the effect of weight loss on the severity of psoriasis. We recruited 60 overweight patients (body mass index 27-40 kg/m2, age 25-71 years, 47% women) with psoriasis of which 53 completed the study. The participants were randomised (1:1) to the intervention or control group. The intervention group received a low-energy diet (800-1000 kcal/day) for eight weeks to induce weight loss, followed by eight weeks of gradual reintroduction of normal food intake, reaching 1,200 kcal/day. The control group was instructed to continue eating ordinary healthy foods. Psoriasis Area and Severity Index (PASI) was used to assess the severity of psoriasis. The median PASI for all patients was 5.4 (interquartile range 3.8-7.6) at baseline. At week 16, mean body weight loss was 15.4 kg (95% confidence interval [CI] 12 to 18, $P < 0.001$) greater in the intervention group than in the control group, with a corresponding mean difference in PASI of 2.0 (95% CI -0.1 to 4.1, $P = 0.06$) in favour of the low-energy diet. In conclusion, treatment with a low-energy diet showed a trend in favour of a clinically important PASI improvement in overweight patients with psoriasis. Long-term studies with more participants are needed to determine the importance of weight loss for treatment of psoriasis in overweight patients.

1075

Detection of blood involvement in cutaneous T cell lymphoma: Spectrum of clinical practice and reliability of blood markers

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Peripheral blood involvement in cutaneous T cell lymphoma (CTCL) has significant prognostic importance. While the spectrum of clinical tools used for blood assessment is vast, we have poor insight regarding the variability of these practices between institutions. Furthermore, few studies have demonstrated how markers for blood involvement compare to one another in measures of performance (sensitivity, specificity, positive predictive value, negative predictive value). A survey study was initiated to members of the USCLC to characterize clinical practices for checking blood in CTCL. Concurrently, a retrospective analysis of peripheral blood analyses from 150 patients seen at the Yale Cutaneous Lymphoma Center between April 2011 – June 2012 was conducted to compare the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for individual parameters (CD4/CD8 ratio ≥10, %CD4+/CD26- ≥ 30%, %CD4+/CD7- ≥ 40%, TCR gene rearrangement via PCR, TCR V-beta restriction) as compared with a gold standard of ISCL-criteria for B2 blood rating. Thirty-three institutions responded to the survey. Fifteen percent of responders indicated utilizing V-beta analysis, 80% utilizing PCR, 100% utilizing flow cytometry, and 55% obtaining Sezary counts. Screening for blood involvement began as early as stage IB for over 50% of respondents. Individually, the parameter CD4+/CD7- ≥ 40% possessed the highest specificity and PPV for blood involvement while %CD4+/CD26- ≥ 30% possessed the highest sensitivity and NPV. However, within the population of patients with a V-beta restricted clone, the specificity and PPV of all three parameters (CD4/CD8 ratio ≥10, %CD4+/CD26- ≥ 30%, %CD4+/CD7- ≥ 40%) was 1.0. While there is currently great inter-institutional variation in clinical practices used to detect blood involvement in CTCL patients, the value of tools such as V-beta may be currently understated and should continue to be judiciously evaluated.

1076

Noninvasive assessment using optical technology of acellular dermal matrices prepared by two different methods. Histopathological correlation

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Severely burned patients need early skin grafting. For those patients, with limited available donor sites, accessibility to living skin equivalents and decellularised allograft dermis would greatly help. The aim of this study is the noninvasive assessment by High-Definition Optical Coherence Tomography (HD-OCT) and Reflectance Confocal Microscopy (RCM) of skin allograft before and during the preparation of human acellular dermal matrices (HADMs) by two different methods. Cryopreserved allogenic human split-thickness skin was used to prepare HADMs. To remove the epidermis the allogenic samples were incubated either with DispaseII or with 1M NaCl. To obtain acellularity the dermal matrices were subsequently incubated with either 0.5% TritonX-100 or 0.1% sodiumdodecylsulfate (SDS) for 24h. The several preparation methods, DispaseII/TritonX-100, DispaseII/SDS, NaCl/TritonX-100 and NaCl/SDS were compared for ease of epidermal removal, cellularity and quality by HD-OCT and RCM and correlated with histopathology. Preliminary results indicate that DispaseII and 1M NaCl are equally efficient in de-epidermization. HADM obtained by DispaseII/SDS is completely acellular but the quality is pore due to elastic fibre fragmentation and decreased number of vascular holes. HADM obtained by NaCl/TritonX-100 is not completely acellular but the quality is good due to the small impact on the collagen and elastic structures and vascular spaces. This experiment shows that each processing step affects in some way the acellularity/quality of the HADMs. Care must be taken in choosing appropriate processing steps to maintain selected properties of the extracellular matrix.

1077

Characterization of adipose tissue inflammation may link psoriasis and cardiometabolic disease

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There is an increased prevalence of cardiometabolic diseases (CMD) such as dyslipidemia, insulin resistance and obesity in psoriasis (PSO), however, the link is poorly understood. Adipose tissue inflammation has been shown to be associated with CMD, but has never been examined in PSO. Therefore, we assessed the presence of adipose tissue inflammation and cellular composition from PSO patients. We collected subcutaneous adipose tissue from non-diabetic PSO (N=11) and non-PSO (N=5) patients. As a comparison for adipose tissue analyses, we also obtained lesional and non-lesional skin from PSO. Adipose tissue protein levels were measured using a Mesoscale Discovery Sector instrument. Flow cytometry of adipose tissue was performed (LSRII) using markers for BDCA-2, CD3, CD14, CD16, CD19, CD11c, CD56, CD206 and HLA-DRII. Mean age (47 +/- 21 PSO vs 48 +/- 19 non-PSO), gender (64% females vs 80%) and body mass index (29.5 +/- 7 PSO versus 27.7 +/- 4 non-PSO) were not statistically different between groups. PSO patients had a median BSA of 4% (interquartile range (IQR) 1.1-7%), mean PASI 8.6 +/- 12.4, were mostly on only topical therapy and demonstrated systemic insulin resistance (median HOMA-IR 2.5, IQR 1.7-4.0). As expected, levels of GM-CSF (23.5-fold), IFN-γ (3.1-fold), IL-12p70 (2-fold), IL-1β (20.2-fold), IL-2 (24-fold), IL-6 (13.6-fold), IL-8 (99.2-fold) and TNF-α (7.8-fold) were higher in lesional compared to non-lesional skin in PSO. In adipose tissue, levels of GM-CSF (2-fold), IL-1β (6.6-fold), IL-6 (1.4-fold) and IL-8 (21.8-fold) were greater in PSO patients compared to controls. Finally, there were distinct populations of CD14+HLA-DRII+CD206- M1 (28% of CD14+ cells) and CD14+HLA-DRII+CD206+ M2 (67% of CD14+ cells) macrophages within adipose tissue from PSO. Our findings demonstrate the presence of adipose tissue inflammation in PSO for the first time in humans, which may be mediated by local macrophage subpopulations. These results suggest that adipose tissue inflammation may contribute to CMD in PSO, however larger studies are needed for confirmation.

1078

Selective cryolysis of sebaceous glands

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Lipid rich tissue is preferentially sensitive to cold injury. The purpose of this study was to evaluate the feasibility of selective injury to the sebaceous gland using controlled cooling of the dermis to sub-zero temperatures. A murine ear model was chosen given the relatively high density of sebaceous glands and ease of access to treatment site. Animals were placed under anesthesia prior to treatment. Each mouse ear was placed on a thermoelectric cooling plate and cooled with various treatment parameters including temperature, duration, cooling and re-warming rates, coupling medium and number of freeze-thaw cycles. The endpoint of this study was histologic evaluation of tissue at various post-treatment time points. Selective sebaceous gland injury, with minimal non-specific injury to surrounding tissue was achieved with certain combinations of cooling parameters. Parameters that increased the extent and specificity of tissue damage include lower target temperature, rapid cooling rate, absence of an external coupling medium, and an increased number of freeze-thaw cycles. The absolute duration of cooling had no significant effect on the treatment outcome. Histologic evidence of preferential injury to the sebaceous glands was evident at 48 hours, peaking at 72 hours as evidenced by loss of sebocyte cytoplasmic details, and an eosinophilic necrotic plug present within the gland. Over 60% of glands were damaged at 72 hours. Histologic appearance of remaining glands by 7 days was normal, but the total number of glands was decreased at 72 hours and 1 week following treatment, suggesting permanent attenuation in gland number. In vitro data using an immortalized sebocyte cell line confirm sensitivity to cold and suggest that cold-induced apoptosis accounts for cell death. The present study demonstrates the feasibility of selectively damaging sebaceous glands in a murine model by cooling at the skin surface, with minimal non-specific damage to surrounding tissue. This approach may serve as a potential therapeutic option for acne vulgaris.

1079

A multiplexed MRM assay panel for high throughput protein quantification in human skin samples

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The multiplexed quantification of proteins in human skin samples has become of great interest in dermatology research. Currently used methods mainly include antibody-based techniques such as immunostainings and western blots. These highly sensitive methods have the drawbacks of lengthy assay development, low multiplexing possibilities, and they are often only semi-quantitative. Emerging mass spectrometric method - multiple reaction monitoring (MRM) - overcomes these limitations enabling method development for new proteins within 6-8 weeks, simultaneous quantification of over 100 targets and flexibility in terms of target composition. Here we report the development of an MRM method for quantification of over 100 proteins in human skin tissue samples as well as in keratinocytes. A comprehensive MRM assay library was generated from samples of human epidermis and dermis. Proteins were extracted from the skin layers, digested to peptides and subjected to mass spectrometry. We assembled a robust panel of MRM assays containing proteotypic peptides representing more than 100 proteins that can be quantified in a single LC-MRM run. The proteins are grouped into areas of interest. We present a simple MRM proteomics workflow that allows high-throughput profiling of over 100 proteins per sample in one LC-MRM run. The proteins are quantified label-free with a median CV below 15% among technical replicates. The proteins in the panel comprise differentiation markers (keratins 1, 2, 5, 10, 14, 15; filaggrins 1, 2), stress markers (heat shock proteins), apoptosis-related proteins (caspase-14), proteins involved in detox/antitox processes (GSTs, superoxide dismutase), proteins relevant to barrier function of the skin (desmoplakin, filaggrin, envoplakin) as well as many other proteins relevant to a wide range of skin diseases, skin metabolism, and other areas of interest. The developed method is best suitable for biomarker discovery, mode of action studies as well as for a wide range of clinical research applications.

1080

Cutaneous squamous cell carcinoma derived cell lines are more sensitive to the proteasome inhibitor bortezomib than normal skin cells

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The proteasome mediates the degradation of multiple proteins, including many key regulators of processes of relevance to cancer. The proteasome inhibitor bortezomib has been approved for the treatment of multiple myeloma and relapsed mantle cell lymphoma. Efforts are ongoing to use bortezomib for the treatment of solid tumours. We are investigating the therapeutic potential of bortezomib for cutaneous squamous cell carcinoma (cSCC). We have compared the effects of bortezomib on normal human keratinocytes and fibroblasts and low passage cSCC cell lines derived from immunocompetent patients (SCCIC 1, 12 and 18) and recessive dystrophic epidermolysis bullosa patients (SCCRDEB 2 and 3). 48 hour incubation with bortezomib selectively kills cSCC cell lines. Bortezomib also selectively blocks colony formation by cSCC derived cells. The level of accumulation of ubiquitin conjugates in normal and cSCC cells is similar. This indicates that the proteasome is inhibited in both normal and tumour cells and that selectivity for cSCCs is unlikely to be due to differences in the entry of bortezomib into cells. The differential effects on viability are associated with a greater upregulation of pro-apoptotic genes in cSCC cells. These studies support further investigation of the potential of bortezomib and newly developed second generation proteasome inhibitors for the treatment of non-RDEB and RDEB cSCC.

1081

Aurora-A overexpression predicts poor outcome in melanoma

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The aim of the study was to evaluate the putative role of AURKA gene (20q13.3) in the progression of melanoma. The Aurora A protein is involved to centrosome function, mitotic entry and spindle assembly. Copy number gains of AURKA were analyzed in 84 melanomas by multiplex ligation probe amplification method. Clinicohistopathological characteristics and BRAF status were added to the analyses. Aurora A was assessed in a tissue microarray containing 189 tumours including 62 from familial melanoma cases. Aurora A expression results were combined to clinicohistopathological characteristics and survival data of patients. Gains of AURKA were observed in 35.7% (30/84) of cases. The alteration was not associated to clinicohistopathological characteristics of tumours. In contrast, presence of BRAF mutation was inversely associated to AURKA gains (p=0.023). Positive Aurora A immunostaining was detected in 56.3% of 112 evaluable cases. Protein positivity was not associated to clinicohistopathological data of tumours. In contrast, Aurora A overexpression was associated with worse overall survival (p=0.04). Patients with no expression of Aurora A showed an increased survival time compared to those patients with Aurora A expression (mean survival of 112.8 months: 95% CI, 97.9-127.7, versus 153.8 months: 95% CI, 137.2-170.5; p=0.044). Furthermore, Aurora A expression was associated with overall survival in thin tumors (Breslow ≤1mm). The study suggests that Aurora A dysregulation might contribute to genetic instability in melanoma resulting in aggressive tumors and shorter survival in a subgroup of patients with early stage disease.

1082

Propranolol cellular targets in infantile hemangiomas

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Propranolol, a non-specific betablocker, is highly effective for the treatment of infantile hemangioma (IH) at pharmacological doses, suggesting a receptor-mediated effect, but its mechanism of action and cellular targets remain unclear. The purpose of our study was to evaluate the expression of beta1, 2 and 3 adrenergic receptor (ARs) in IH tissue samples. Immunohistochemical staining of beta1, 2 and 3 ARs was performed on 33 GLUT1+ IH samples obtained after informed consent, at various evolutive (3 in proliferative, 10 in early involutive and 21 in the late involutive phase) and treatment stages (11 treated with propranolol) and control tissues from placenta (1), and non propranolol responsive vascular tumours: non-involuting (5), rapidly involuting congenital hemangiomas (3) pyogenic granulomas (2). Positive cells were identified by double immunofluorescence staining using CD31, CD34, alpha-SMA and tryptase. Semi-quantitative assessment of markers was done on 4 representative fields at 400x magnification. Beta1ARs were highly expressed in endothelial cells (CD31+ CD34+) and pericytes (alpha-SMA+) of capillary vessels of IH, and a low expression was noted on mast cells (tryptase+). Beta2ARs were very highly expressed on mast cells and a moderate expression was found on endothelial cells and pericytes. Beta3ARs were weakly expressed in endothelial cells, and were mostly detected on adipocytes at the involutive stage IH. There was no obvious difference in type of cells expressing and the intensity of expression of beta1 and 2ARs according to stage, and between treated and untreated IH, and between IH and control vascular tumours except for mast cells not present in placenta. To conclude, our study identified several potential target cells for propranolol therapy in IH, but a receptor type/cell type for IH was not clearly dominating, suggesting that functional receptor status/cell status may be important to elicit pharmacological responses, or that indirect effects occur via other cell types.

1083

Antibody formation to adalimumab in the treatment of psoriasis vulgaris is most often seen before 24 weeks of treatment and has great influence on clinical efficacy: One year data in 59 patients

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In a previously reported cohort of 29 patients with plaque type psoriasis followed for 24 weeks, clinically relevant antibody formation to adalimumab was frequently found (Lecluse 2010). We now present the extent and clinical consequences of antibody formation against adalimumab in the treatment of 59 patients followed for 1 year. From 59 consecutive patients treated with adalimumab for plaque type psoriasis at the department of dermatology in the participating centres, the disease severity (measured by PASI) was assessed at baseline, week 12, 24 and 52. At these moments blood was drawn at an adalimumab trough level. Adalimumab (ADA)- and antibody (ATA) concentration was determined. A correlation was calculated between clinical response, ADA- and ATA concentration. In total, 45.8% of patients formed ATA, 10 patients before week 12, 14 patients between week 12 and 24 and 3 patients between week 24 and 52. The Spearman`s rank test showed a correlation between ADA concentration and ATA concentration, clinical efficacy and ATA concentration and ADA concentration and clinical response of -0.824, -0.561 and 0.578 respectively. 5 patients were treated with methotrexate concomitantly, one of them formed (low) ATA. This study shows that patients who do not develop ATA in the first six months of treatment have little chance of developing antibodies the following six months. Conform patients with rheumatoid arthritis, also in patients with psoriasis there is a trend of less antibody formation with concomitant methotrexate.

1084

Therapeutic benefit of topically applied ascorbic acid in basal cell carcinoma

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In our pilot study we investigated potential efficacy of topically applied high-dose ascorbic acid in human basal cell carcinoma (BCC). Although systemic vitamin C has been reported to be beneficial in the management of advanced cancer and regarding skin tumors there are some published data on its toxicity to melanoma malignum, studies investigating sensitivity of BCC as the most common skin cancer are lacking. Six patients with a total of seven (one solid, six superficial) lesions of histologically certified BCC were topically treated with ascorbic acid oversaturated solution for a 22-week-long period. Following treatment a control punch-biopsy and histological examination were performed referring to therapeutic responsiveness. Five (one solid, four superficial) of the seven lesions proved to be tumor free by control histology which described scar tissue in four samples and aspecific dermatitis in one case. The other two specimens still contained few basaloid tumor nests, although a size-reduction of the tumor and a prominent scarring were also detected. At a 12-month follow-up visit we found tumor recurrence in two successfully treated superficial lesions (one in the marginal zone and one along the linear scar). Our data highlight the potential antitumor effect of topically applied vitamin C in human BCC. Result seems to develop slowly and the lesions heal with scarring. Tumor recurrence may be expected in the untreated perilesional region. Further clinical investigations with more patients involved would be necessary to confirm and further complete our primary observations.

1085

Short-term *in vivo* protocol and multiphoton microscopy: Non invasive assessment of the effects of retinoids

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The occlusive patch test initially developed for assessing the effects of topical retinoid on human skin[1], has been extended as a short term protocol for screening anti photo-aging agents[2, 3]. In the protocol, biopsies are performed at the end of the occlusion period for immuno-histochemical analysis. Our objective was to assess whether, in this test, in vivo multiphoton microscopy (MMP), a new non invasive skin imaging technique, could be used for assessment overcoming the necessity of invasive biopsies. Accordingly, a pilot study was performed involving 5 healthy female volunteers, aged 55-65 years. 0.025% Retinoic acid (RA) and 0.3% Retinol (RO) were applied under occlusive patches on the dorsal side of their forearms, for 4 days (D8-D12) and 12 days (D1-D12), respectively, as previously described[3]. The patch alone was applied to a third area, as control. The 3 areas were imaged at D0, D12 (end of the occlusion period), D18 and D32 using the DermaInspect® device by taking advantage of intrinsic MMP signals from cells, and elastic and collagen fibers. The following quantitative parameters were extracted thanks to a 3D image processing recently developed[4]: epidermal thickness, normalized area of the dermal epidermal junction (DEJ), density of melanin. RO treated area showed a marked thickening of epidermis (5/5), a slightly more undulated DEJ (5/5) and a slight decrease in the melanin content at D12 (5/5) followed by a rebound at D32 (4/5). No change in these parameters was observed with RA which was applied for 4 days (versus 12 for RO) to avoid irritation caused by extended occlusion. Qualitative alterations of the stratum corneum were observed with both products whereas occlusion alone did not modify any of the parameters. This pilot study shows that short term screening protocol combined with in vivo MMP allows non invasive detection of some cutaneous effects induced by retinoids. This method could be useful in the screening of anti-ageing or whitening agents. Ref: [1]Griffiths, BrJDerm 1993; [2, 3]Watson, JID 2001 & BrJDerm2008; [4]Baldeweck, SkinTecRes in press

1086

***In vivo* multiphoton microscopy assessment of topical corticosteroid-induced skin alterations with age**

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In a recent pilot study, multiphoton microscopy (MMP), a new non invasive skin imaging technique, was shown allowing corticosteroid-induced skin side effects to be early detected[1]. The present study aimed at assessing the dynamics of onset of these effects according to age. 12 human female volunteers including 2 age groups of 6, i.e. younger (Y:18-25y) and older (O:70-75y) were topically treated with clobetasol propionate and control vehicle on 2 small areas of their inner forearm under occlusion for 9 days. The treated areas were imaged at D0, D2, D9 (end of the treatment) and D28 using the DermaInspect® device by taking advantage of intrinsic MMP signals from cells, and elastin and collagen fibers. Several quantitative parameters were extracted from epidermis and superficial dermis thanks to a recently developed 3D image processing[2]. Main results were: i) a decrease in epidermal thickness in both groups ($p<0.0001$ at D9) ii) a flattening of the dermal epidermal junction in the Y group. As for these two parameters, the values in the younger group at D9 became comparable to those of the older group at D0 iii) a slight decrease in the melanin content in both groups associated with a visible whitening which was confirmed by colorimetry iiii) an increase in elastin content corresponding to an elastosis-like alteration in the superficial dermis in the Y group. Qualitative modifications of the stratum corneum were observed in both groups (O>Y) whereas occlusion with control vehicle did not alter any of these parameters. All the alterations were shown reversible at D28. This short-term induced reversible atrophy combined with MMP appears a promising non invasive model for assessing in vivo the atrophogenic effects of corticosteroids which seem mimicking senile atrophy. Additionally this short-term protocol could topically address the potential of products that may counteract such induced atrophy and be of valuable help in the screening of whitening agents. Ref:[1]Ait El Madani, JBO 2012, [2]Baldeweck, SkinTecRes in press

1087

The diagnosis of sezary syndrome established by T-plastin, twist, CD158k/KIR3DL2 and NKp46 gene expression

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Several molecular markers including T-plastin (PLS3), transcription factor Twist, CD158k/KIR3DL2 and NKp46 (CD335) have been specifically identified in patients with Sézary Syndrome (SS), the erythrodermic and leukemic form of cutaneous T-cell lymphoma (CTCL). Our purpose was to investigate whether the expression profiling of these four genes by quantitative Real-time PCR (qRT-PCR) can be employed for the diagnosis of SS. A cohort of 81 patients with SS was investigated for tumor burden and mRNA expression quantification of PLS3, Twist, KIR3DL2, and NKp46, in whole PBMC and CD4+-purified T cells from blood samples using SYBR Green qPCR and specific primer pairs. CD4+-purified T cells from 12 healthy donors were studied as controls. QRT-PCR mean values (±SD) of PLS3, Twist, KIR3DL2, and NKp46 mRNA levels of control CD4+-purified T cells reached 2.4±2.5, 6.6±8, 22.5±20.4, and 2.6±2.8, respectively, and allowed a respective threshold of 95% significance, any value less than the respective threshold being considered as negative. As positive controls were used mRNA mean levels (±SD) detected in SS HuT-78 cell line (128±65 for PLS3, 13155±3000 for Twist, 316±40 for KIR3DL2), and in NK-purified cells (n=3) with 371±80.2 for NKp46. Our results demonstrated that CD4+-purified T cells from SS patients expressed PLS3, Twist, KIR3DL2, and NKp46 mRNA mean levels (±SEM) of 726±144, 1,511±312, 878±102, and 7.4±1.8, respectively. The accuracy was 100% in identifying these samples as SS patients since the four markers were detected in 20% CD4+-purified T cell samples, three ones in 53%, two ones 20% and only one marker (Twist, PLS3 or Nkp46) in 7%. Of interest, mRNA extracts from whole PBMC gave mean values (±SEM,n=48) of 620±427 and 538±219, respectively, and thus can be used in routine for PLS3 and Twist mRNA detection. These results clearly demonstrate that gene expression profiling by quantitative PCR on a selected number of 4 critical genes can be employed for the molecular diagnostic of SS.

1088

Successful control of adverse events associated with vismodegib treatment of advanced basal cell carcinoma by recognition of hedgehog pathway activity in normal adult tissue

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The hedgehog (HH) pathway is believed to be active primarily in fetal tissue, basal cell carcinoma (BCC), and medulloblastoma. Nevertheless, recent publications reveal the HH pathway contributes to normal adult hair, olfactory, stomach, and muscle organ function. Although the adverse events (AE) associated with vismodegib may lead to discontinuation of treatment, no standard approach exists to intervene against these AEs. Twenty two patients were treated with vismodegib for advanced BCC. Each patient who experienced an AE was advised to respond according to the theoretical mechanism by which HH inhibitors block normal HH pathways in the affected organ system. Patients began the interventions within 1-2 months of starting vismodegib, as follows: Alopecia: to stabilize Ca flux in normal hair disrupted by vismodegib, patients used zinc (Zn) based shampoo and/or minoxidil foam. Dysgeusia: to release Ca accumulation in taste bud cells, they used Zn lozenges; to promote arrested olfactory HH pathways, they drank caffeinated beverages. Nausea: to replace presumed reduction in stomach acid production, patients drank acidic liquids with each meal. Muscle cramps: to block Ca retention associated with interrupted muscle dependent HH pathway, they used calcium channel blocking agents, Mg, and /or adequate hydration. Clinical responses to the interventions were assessed by chart review. Patients were on vismodegib from 2-24 months. The number of patients who stabilized, improved, resolved, or prevented the AE: alopecia 11 of 12; dysgeusia 14 of 16; nausea 5 or 5; muscle cramp 10 of 10. Not all patients experiencing these AEs followed the treatment; of those who did compliance varied. All patients were able to control the AEs to within tolerable levels. No patient stopped vismodegib due to these AEs. Recognition that HH pathway functions in normal adult tissue may explain and allow treatment of AEs associated with use of vismodegib.

1089

Transcriptome analysis reveals that severity of psoriasis is correlated with expression of genes involved in epidermal differentiation and proliferation

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All published studies of the psoriasis transcriptome have demonstrated marked differences in gene expression between diseased and normal skin. However, no study has yet evaluated the correspondence of disease severity and gene expression. To address this, gap, we analyzed the correlation between the psoriasis area severity index (PASI) of the biopsied lesion and gene expression levels measured by RNAseq. Analysis was restricted to genes whose median expression in 92 lesional vs. 82 normal skin biopsies differed significantly by a factor of at least 2, and to 66 cases for which complete PASI data were available. Using a false discovery rate threshold of 0.1, we identified 34 genes whose expression levels were significantly correlated with PASI. All 11 up-regulated genes were positively correlated with PASI, and all but one of the 23 down-regulated genes were negatively correlated. The strongest negative correlation with PASI was seen for UPK1A (Uroplakin 1a), which is expressed in the epidermis in addition to the urinary tract. Other down-regulated genes whose expression was negatively correlated with PASI included CTSL2 (cathepsin L2), FLG and FLG2 (Filaggrin and Filaggrin 2), all of which are involved in epidermal differentiation, and STXBP6 (amisyn), which has been shown to be associated with good response of rheumatoid arthritis to TNF blockade. An up-regulated gene whose expression was positively correlated with PASI was WNT5A (wingless-type MMTV integration site family, member 5A), which is involved in keratinocyte differentiation. Among the individual components of the PASI score (erythema, desquamation, and induration), significant correlations with gene expression were seen only for desquamation. These observations could help us understand the pathogenesis of these individual phenotypes, and also to develop a better psoriasis severity scale for assessment of disease and treatment.

1090

Involvement of the IL-23/TH17 pathway in non melanoma skin cancers

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Few recent studies investigated the role of the IL-23/Th17 axis in human carcinogenesis but no studies are currently available for NMSCs. Aim of the present study was to evaluate the expression of IL-23, IL-17, IL-22 and INFγ at the gene and protein level in NMSCs and to analyze their correlation with the clinicopathological features. Immunohistochemical and gene expression analysis was carried out in 41 basal cell carcinomas (BCCs) (13 superficial BCC, sBCC; 28 nodular BCC, nBCC) and in 37 in situ squamous cell carcinomas (isSCCs: 21 actinic keratosis and 6 Bowen's disease). Nine samples of normal skin were used as controls. Immunohistochemical level of IL17 was significantly higher in nBCC as compared to sBCC while IL23 and IFNγ levels were increased in sBCC as compared to nBCC. IL17 was highly expressed in ulcerated BCC vs non ulcerated BCC, whereas no differences were observed for IL23 and IFNγ expression in these subtypes. The Spearman correlation analysis showed a positive correlation between both IL-17 and IL23 expression and the peritumoral inflammatory infiltrate. Interestingly, high level of IL17 expression correlated with high levels of IFNγ expression. Molecular analysis demonstrated that IL-23 mRNA level was 18-fold increased in BCCs as compared to normal skin ($p<0.0001$) and 2-fold increased as compared to isSCC ($p<0.0001$). A trend towards an increase of IL17 and IL22 expression in BCC as compared to isSCC and normal skin was also observed. Interestingly, IL17 and IL22 mRNA levels were significantly higher in nBCC as compared to sBCC ($p=0.0360$, $p=0.0145$). Finally, mRNA INF-γ levels were increased in BCCs ($p=0.0005$) and isSCCs ($p<0.0001$) vs normal skin, but no significant differences were observed with regard to specific clinico-pathological features. Our results support the involvement of the IL23/Th17 pathway in the pathogenesis of NMSC.

1091

Automated evaluation of actinic cheilitis severity by measurement of lip border irregularity

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Actinic cheilitis (AC) is common, affecting mostly the lower lip. A distinct clinical feature of AC is lip border retraction and the development of irregularity. Objectives: To develop a lip border irregularity index as a diagnostic and severity feature of AC employing computer vision techniques. Material and Methods: Images of 14 AC patients and 26 controls were included. 6/14 patients were also evaluated for disease severity prior to and 6 months after treatment with immunocryosurgery. Following preprocessing for light and scale variations, images were transformed from RGB to YIQ color space and Q color channel retained for further lip processing. A spatial fuzzy C-means clustering algorithm was employed to segment lower lip area. Quantification index of AC was calculated as the distance of the extracted lower lip border from "normal" lower lip border. "Normal" border was modeled as the symmetrical four degree polynomial border that best fits data lip points set, consisting of lip corners and maximum peaks detected from lesional lip border. Receiver operating characteristics (ROC) analysis was performed to assess the diagnostic efficiency of the proposed index. Results: The developed lip irregularity index yielded area under the ROC curve of 0.98 suggesting a high diagnostic value. AC was diagnosed with 92.8% sensitivity and 100% specificity. Furthermore, all 6 patients treated showed reduction of the lip border irregularity index corresponding to the observed clinical improvement of AC. Conclusions: The introduced irregularity index demonstrates efficacy in the quantitative differentiation of healthy and AC lips and could be a valuable automated tool in clinical practice and research.

1092

A compressed collagen hydrogel results in a mechanical stable, non-contracting *in vitro* skin substitute that enables the integration of a vascular tube and a structured dermal-epidermal junction

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Here we describe the development of a refined in vitro skin substitute (ivSS), with enhanced mechanical properties and a perfused vascular structure. We developed a custom made system that is able to compress collagen hydrogels (CHG), seeded with human dermal fibroblasts (hDF), with a defined force and velocity. Using our system with a maximum force of 20 N the mechanical properties of CHG could be adjusted to reach comparable stress-strain curves as human dermal biopsies. The change in the mechanical properties also led to a highly decreased self-contraction of the CHG. During a culture period of 14 days the wet weight of uncompressed CHG decreased by 80%, whereas the wet weight of compressed CHG decreased by 25%, which was not induced by a loss of hDF viability as proved by (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and live-dead staining using Propidium iodide and Fluorescein diacetate. The higher mechanical resilience and decreased self-contraction also enabled us to induce further anatomical features to the ivSS. Using an elastic impression of human skin samples we could imprint a structured dermal-epidermal junction on to the ivSS. Additionally, a vascular structure could be embossed into the collagen, which could be reseeded with human dermal microvascular endothelial cells and connected to a physiological medium flow. The refined ivSS can be used as a long-term skin model or as a non-contracting skin coverage for clinical applications.

1093

Downregulation of DNA repair by an antimycotic drug leads to a phenotype resembling Xeroderma pigmentosum and increased skin cancer

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Prophylactic protection of patients with severe immunosuppression such as bone marrow transplantation individuals is of vital importance to shield the patient from opportunistic fungal infections. It has been reported, that an antimycotic drug used for this purpose may increase the risk of subsequent development of skin tumors. Here we report, that treatment with this antimycotic drug leads to suppression of the DNA repair mechanism nucleotide excision repair (NER) in cell based assay (such as Unscheduled DNA Synthesis and Comet assay) and increases DNA damage. Individuals with a genetic defect in NER develop Xeroderma pigmentosum, a rare skin disease, clinically characterized by pigmentary changes and a 1000 fold increased skin cancer risk. Interestingly, patients treated with this antimycotic drug develop a clinical phenotype that closely resembles that of XP. Patients develop pigmentary changes as well as skin tumors such as squamous cell carcinomas, thus reporting the link between this antimycotic drug and symptoms of NER. Importantly the repair suppressive effect was transient since removal of antimycotic drug eventually lead to normalization of all repair associated parameters. Further studies are necessary to elucidate the full effect of antimycotic prophylaxes (i.e. time to tumor development). These findings indicate that it is important to screen patients with severe immunosuppression and antimycotic prophylaxes for early indications of an XP like phenotype as potential early warning for the development of skin tumors.

1094

Increased frequency of diabetes mellitus in patients with pemphigus

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Pemphigus is an autoimmune disease characterized by autoreactive T and B cells specific for the intercellular junctions of keratinocytes. The presence of one autoimmune disease could increase the risk for additional comorbidities with immune-mediated or inflammatory pathogenesis. The objective of the present study was to evaluate the comorbidity profile in patients with pemphigus. Therefore, we performed a hospital-based case-control study on 132 patients with pemphigus and 250 gender- and age-matched patients with skin diseases other than autoimmune bullous diseases. The median age at diagnosis for patients with pemphigus was 52 years (range 15-87). The sex ratio was female:male 1.58. Of the 132 patients diagnosed with pemphigus, 15 (11.36%) died within 22.6 months, 7 of them (5.3%) within the first year after hospitalization. Diabetes mellitus was significantly more frequent in pemphigus patients compared to controls (7.57% vs. 2.8%, odds ratio 2.84, 95% confidence interval 1.05-7.65; p=0.03). Five patients developed diabetes after the initiation of corticosteroid therapy, 3 within the first year. Patients with pemphigus presented with the following comorbidities: arterial hypertension (21.21%), coronary diseases (7.57%), other cardiovascular disorders (5.3%), other autoimmune diseases (3.03%), dental problems (25.75%), smoking (11.36%). In conclusion, in our patient cohort, pemphigus was more frequently associated with diabetes mellitus at diagnosis, which might due to the presence of a shared genetic risk and/or common inflammatory pathways of these two diseases. The association of pemphigus and diabetes mellitus could favor the occurrence of different complications, especially after the initiation of corticosteroid therapy.

1095

Transcriptome profiling identifies novel functions of acitretin in human epidermis

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Acitretin is a systemic retinoid used for the treatment of psoriasis including pustular psoriasis, pityriasis rubra pilaris, other inflammatory skin disorders and inherited disorders of keratinization (mainly ichthyoses and palmoplantar keratodermas). Although teratogenic, it is still a valuable drug in dermatology clinical practice. In this study, we used RNASeq to identify transcriptomic changes in human epidermis treated with acitretin or the retinoic-acid metabolising binding agents (RAMBA), talarazole and liarazole. Human epidermal skin equivalents were pre-treated with retinoic acid and subsequently treated with 2.5 μM acitretin, talarazole or liarazole. RNA extraction was performed from triplicate biological replicates. Following library preparation, fragmentation and sequencing, initial analysis was performed using ArrayStudio 6.1. One way ANOVA, p value <0.01, revealed 108 genes upregulated and 86 genes downregulated in the acitretin group compared to control untreated epidermis. Functional classification of downregulated genes using DAVID revealed changes in keratins, carbohydrate-binding genes, inflammatory response genes and apoptosis regulatory genes. Upregulated genes included cell-cell adhesion molecules, cell cycle regulatory genes, zinc finger genes and proteases. With this stringent analysis, just 2 genes were upregulated and 1 downregulated in the RAMBA subgroups compared to control. Further analysis and correlation with whole genome methylation data obtained in parallel is in progress. These data give further insight into how acitretin affects normal epidermal physiology.

1096

Physical activity and diet affect systemic inflammation and severity of psoriasis

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Psoriasis is a systemic inflammatory disorder affected by lifestyle choices such as diet and exercise. Exercise and dietary antioxidants including vitamins, minerals, whole grains, fruits, and vegetables have anti-inflammatory effects. We studied the physical activity and cardiovascular risk biomarkers of 30 patients and performed a 24-hour dietary recall on 94 patients with psoriasis. Patients in the physical activity study had a median PASI of 12.8 and 19/30 (63%) were obese. Pedometer measurements averaged over 7 days identified 19/28 (68%) who were somewhat inactive or sedentary (<7,500 steps/day). Higher pedometer readings associated with lower PASI, BMI, waist/hip ratio, hsCRP, and LDL levels; however the decreases failed to reach significance. Smokers (10/30) had higher PASI, hsCRP, resistin and dermatology life quality index (DLQI) averages and lower average number of steps/day. Patients with higher DLQI scores and a report of depression on the SF-12 had a positive correlation with higher PASI scores. Those with higher average pedometer readings reported less depression. Obesity is associated with increased inflammation and psoriasis severity. Poor diet and lack of exercise increase risk for elevated BMI. Of the 94 patients who completed the dietary recall, a majority of patients failed to reach recommended dietary allowances (RDAs) for the following antioxidants: vitamins A (65% of patients below RDA), C (60%), D (96%), E (89%), and K (66%); whole grains (94%), vegetables (70%), and fruits (74%). Excess fat intake occurred in 85%, saturated fat in 77%, and carbohydrates in 84% of patients. A majority of patients either failed to meet RDAs of antioxidants including vitamins, whole grains, fruits, and vegetables or exceeded fat and carbohydrate recommendations which may contribute to increased co-morbidities associated with psoriasis. Improving diet and exercise levels leads to decreased inflammation and BMI and may therefore also decrease the severity of psoriasis.

1097

Development of a preclinical model for P-glycoprotein based skin absorptive transport for topical drug delivery-a case study with cyclosporin A

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P-glycoprotein (P-gp/MDR1/ABCB1) is a membrane-associated multidrug transporter of the ABC transporter family and its upregulation results in multidrug resistance of cancer cells. P-gp is also expressed in normal tissue including skin, liver, kidneys, and in endothelial cells. Recently, we reported that epidermal P-gp plays a key role in skin absorptive transport of topically applied anticancer agent PEP005 for eradicating xenografted tumors in athymic mice. Our current study focuses on developing a preclinical model for P-gp mediated skin absorptive transport of a topically applied drug for systemic drug delivery. The drug used for this study is cyclosporin A (CsA), an immunosuppressive drug used in the treatment and prevention of host rejection in transplant recipients, but also for a variety of medical conditions, including psoriasis, Rheumatoid arthritis, and Crohn's disease. CsA is administered intravenously and orally in most cases but occasionally, topically for local treatment. CsA is also a known P-gp substrate. To test if topically applied CsA could reach the blood stream and result in systemic delivery, we applied CsA to the dorsal skin of athymic mice and drew blood to examine blood concentration of CsA using HPLC-mass spectrometry. A dose-response study showed that topical application of CsA above 100 μg resulted in a detectable CsA blood level after 24 hours. CsA was detected as early as three hours after topical application and maintained up to 24 hours then declined. Inhibition of P-gp by pretreatment of the mice with a P-gp specific inhibitor, Tariquidar, reduced blood CsA level. Daily application of CsA (400 μg) was also evaluated for 7 days. A stable blood concentration (~180 nmol/L) was achieved during the 7 day treatment period. Our preliminary results indicate that systemic delivery of CsA can be achieved by topical skin application. To advance these findings, we will use our preclinical model to test topical application of other drugs for local and systemic delivery using P-gp based skin absorptive transport.

1098

Molecular characterization of S.aureus isolated in children with atopic dermatitis

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Children with atopic dermatitis (AD) have their skin colonized by S. aureus more frequently than general pediatric population. In addition, vitamin D has direct beneficial effects on the innate immune system. In this study, we investigate the prevalence of skin and nares colonization by S. aureus in children with AD, the genetic profile of the isolates and their association with allergy, AD severity and serum vitamin D. We performed an observational study in a sample of children diagnosed with AD in two settings: San Jorge Hospital, Huesca and University Hospital Niño Jesus, Madrid. Patients were collected along 2011. Swabs from affected skin and nares were taken for microbiological culture. Pattern of antibiotic resistances and 17 virulence genes of the S. aureus isolates were studied. 102 patients were included in the study with a mean age of 5.94 +4.18 years old. All had skin samples and 75 also nares swabs. 31.4% were found to harbour S. aureus on the skin and this was significantly associated with older age, higher SCORAD, positive Phadiatop Infant (PI) and sampling during the summer in the bivariate analysis. Only PI was associated with an increased risk of colonization by S. aureus in the multivariate analysis (OR 8.67 [IC95% 1.7 to 44.1]. Presence of virulence factors of S. aureus TSST-1, ETA, CAN, AUR and SEC were associated with lower serum levels of vitamin D. The presence of S. aureus on nasal swabs were not associated with any of the variables studied. The results of this study show a low rate of S. aureus colonization of pediatric patients with AD. S. aureus colonization is associated with allergy and determines a higher SCORAD, whereas its virulence factors are associated to vitamin D levels under 30 ngr/ml. Whether all these findings may have implication in treatment remains to be elucidated.

1099

Rapid healing of venous stasis leg ulcers through stimulation of wound edge closure following cultured epidermal autografting

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We previously1 reported the efficacy and durability of wound healing of confirmed chronic venous stasis leg ulcers in a prospective randomized unbalanced clinical trial using the application of a living serum-free cultured epidermal autograft (CEA) in conjunction with wound-area debridement and a four-layer compression wrap (N=10) compared with wound-area debridement and a four-layer compression wrap in patients with hard-to-heal leg ulcers (N=5). The average time to wound closure for the autologous grafted wounds was 4.1weeks for 80% (8/10) of the cases that closed in 12 weeks compared with 12 weeks for only one closed wound in the control case. The graft treatment significantly improved outcome and provided durable wound closure. Here, we report that upon further analysis of the data, there is a significant linear correlation between initial ulcer size-perimeter (cm) and rate of healing (cm-sq/week ($p < 0.05$). These results imply that graft-stimulated healing occurs predominately from wound edges. The CEA take was >90% and wound closure required an average of 1.4 applications per subject to effect complete wound closure. This result is supported by data showing that dermal volume fill rate is also correlated with ulcer perimeter size reduction.1 Wille et al, WR &R 19(4):464-474, 2011

1100

Romidepsin and PUVA therapy in refractory advanced stage CTCL is associated with remission and increased cell death and Fas expression

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The purpose of this study was to determine if addition of psoralens + ultraviolet A (PUVA) to romidepsin (ROM) would be more effective in treating a patient with refractory cutaneous T cell lymphoma (CTCL), compared to ROM alone. Briefly, a 54-year-old female with Mycosis Fungoides stage IIB CTCL progressing on multiple systemic treatments, including 14 cycles of ROM alone, subsequently had marked clearance of disease after 4 weeks of PUVA + ROM. Two residual tumors similar in size and location were identified; one was protected from additional UVA therapy while the other was treated. After 24 hours, both tumors were excised. TUNEL confirmed increased apoptosis in atypical lymphocytes in the tumor receiving UVA. To study the effect of combining of PUVA with ROM on CTCL cells, we titrated UVA (1 J, 0.5 J, & 0 J) and ROM (1.25 nM, 0.25 nM, 0.05 nM, & 0 nM) on Sezary syndrome patient-derived SeAx cells pretreated with psoralens. Cells were incubated for 26 hours, and cell viability was assessed using a CellTiter-Fluor Cell Viability Assay. Our results confirmed that the combination of PUVA + ROM is resulted in fewer viable cells compared to PUVA or ROM alone. To elucidate possible mechanisms of this synergistic increase in cell death, we evaluated the expression of various apoptotic genes in the extrinsic pathway (Fas, cFLIP, TNF-α, TRAIL, & TRAIL-R1) in the presence of various titrations of UVA and ROM using realtime PCR. Our preliminary data showed a synergistic increase in the expression of Fas mRNA at 1 J UVA + 0.05 nM ROM at 24 hours post-treatment compared to each of these conditions by themselves and untreated controls. We were unable to detect a synergistic increase in the levels of the other genes. However, the same trends in Fas expression were observed at 6 hours post-treatment (total n = 3). Our results suggest that PUVA + ROM combination therapy may be an additional option for the treatment of refractory CTCL due to increased apoptosis via synergistic effects on the Fas pathway.

1101

T-cell related cytokine expression from scalp biopsy RNA samples reveals peaks in cytokine expression in peri-lesional alopecia areata (AA) versus lesional and normal scalp suggesting treatments should be directed to this region to impact the AA process

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AA is a complex genetic, immune-mediated disease for which there is no cure. There is a potential opportunity to treat AA with antagonists to specific "differentiation" or "effector" cytokines if the underlying polarity of associated T-cell responses can be defined by a combination of RNA profiling on arrays and RT-PCR for specific cytokines of dendritic cells or differentiated T-cell subsets. In this study, a 53-year-old male with steroid responsive AA, onychodystrophy and Graves disease was advanced to pulse, intravenous Solu-Medrol with 250-ml of D5W infused monthly over 1 hour over 3 consecutive days for 4 months. At baseline and prior to each infusion, two 4-mm scalp biopsy samples were taken from lesional, peri-lesional and adjacent non-lesional scalp for histologic and RNA expression analyses. Unexpectedly, during treatment, the AA process worsened and severity score increased from 69% to 83%. A progressive decrease in the expression levels of several primary T-cell and effector cytokines (i.e., IL-2, IL-2Ra, IL-2Rg, IL-9, IL-13, IL-15, IL-22, IFN-g) in lesional samples occurred possibly representing a cessation of the inflammatory process. A second key finding was higher expression levels for many cytokines and inflammation-related factors in perilesional samples in the second (i.e., IL-12p40, IL-23p19, IL-1B, IL-13, IL-17F, TNF) or third (i.e., IFN-g, IFN-α, IL-2, IL-15, IL-31, JAK3, CD80) biopsy samples, after which the levels dropped for the fourth and final sample. The peak in inflammatory factors in perilesional skin correlated with worsening disease progression. These results point to testing treatments that target cytokines in perilesional skin as inflammation and changes in cytokine expression are most prominent here as compared to normal or lesional skin.

1102

Topical rapamycin therapy is effective against hypomelanotic macules arising in tuberous sclerosis complex: A prospective, self-controlled study

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Tuberous sclerosis complex (TSC) is an autosomal dominant disorder causing multiple hamartomas. The mammalian target of rapamycin (mTOR) inhibitors such as rapamycin are known to be effective against tumors in TSC patients, including angiofibromas. Hypomelanotic macule is a major feature of TSC. We previously reported two cases of hypomelanotic macules in TSC which were improved by topical rapamycin. The purpose of this study is to evaluate the effect of topical rapamycin against hypomelanotic macules in TSC patients. This study was a prospective, self-controlled trial. Six patients with definite TSC were enrolled. 0.2% rapamycin gel was applied to hypomelanotic macules on both sun-exposed areas and non-sun-exposed areas in each patient for 12 weeks. Three dermatologists rated improvements ranged from –1 (worse) to 2 (almost disappeared) compared with baseline. Improvement score (IS) was calculated as the average of their marks. Lightness of skin (L*) was also measured by a spectrophotometer. Decrease of delta L* reflected the improvement of hypomelanotic macules. Blood rapamycin levels were analysed at the end of treatment. Hypomelanotic macules in the sun-exposed areas were significantly improved after 12 weeks treatment (1.44 ± 0.51, $P=0.034$), and the improvements continued until 12 weeks after completion of treatment. Delta L* in the sun-exposed area appeared to decrease after treatment, but not significantly. Meanwhile, the improvements in the non-sun-exposed areas were small (maximum mean IS 0.42 ± 0.20). However, delta L* in the non-sun-exposed areas decreased significantly after treatment. No adverse events were observed, and rapamycin was not detected in the blood of any patient. In conclusion, topical rapamycin is effective and safe against hypomelanotic macules arising in TSC, especially in the sun-exposed areas.

1103

Low-dose local ionizing radiation provides "targeted" therapy and induces durable remission in early stage mycosis fungoides/CTCL

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We recently reported that mycosis fungoides (MF) is a malignancy of resident effector memory T cells (TEM), while Sezary syndrome/Leukemic CTCL is a malignancy of central memory cells TCM with skin homing properties. While low dose-alemtuzumab is a "targeted" therapy for TCM in L-CTCL based on the biological behavior of the malignant cells, an analogous therapy has been elusive in MF. We have found MF to be characterized a by T cells that have low levels of L selectin and variable levels of CCR7 (thus, TEM). In those lesions that are most stable and persistent, low to neglible levels of CCR7 predominate on the non-recirculating malignant T cells. Most recently, we have demonstrated that very low doses of ionizing radiation (e.g., 4Gy x 2) with limited penetration can induce long standing remissions in such stable lesions. A uniquely stable form of MF is syringotropic MF, located on the volar aspects of the palms and soles, often in the setting of chronic hand and foot dermatitis. It is debilitating, nearly always refractory to topical therapy, and causes severe disability. Patients with biopsy proven syringotropic CTCL were treated with a total of 8 Gy in 2 sessions, delivered either by brachytherapy or electron beam therapy. In all cases, such treatment led to complete and durable remission. Interestingly, the associated hand and foot dermatitis in the treated area went into remission as well. This "targeted" therapy is convenient for the patient (three visits), can provide life-changing effects (one patient had not been ambulatory for >1 year), can spare the patient systemic mediations with multiple side effects, and is potentially curative as it targets a non-recirculating population of malignant T cells which are exquisitely sensitive to this mode of therapy.

1104

Identification of gene expression biomarker signatures for use as an Alopecia Areata Disease Activity Index (ALADIN)

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Alopecia Areata (AA) is a highly prevalent autoimmune disease in which the hair follicle is attacked by cytotoxic T lymphocytes. The accessibility of the target organ within skin biopsies has provided us the opportunity to develop a novel disease activity score based on quantitative composite gene expression signatures. Using both Affymetrix microarrays and RNA-Seq data analyzed using Ingenuity Systems' IPA, we identified two striking gene expression signatures in total skin from both human AA and the C3H-HeJ mouse, namely the IFN response, including IFN-gamma and IFN-inducible chemokines, and a cytotoxic T cell (CTL) signature including CD8 and granzymes, implicating these effectors as the dominant inflammatory cells in AA pathogenesis. To generate a functional biomarker from the AA transcriptome, we developed the Alopecia Areata Disease Activity Index (ALADIN), a two-dimensional quantitative composite score. ALADIN was derived from expression levels of representative genes from both the IFN and CTL pathways to generate a measure of the distance of AA transcriptional levels from a baseline obtained from the skin of healthy individuals. The ALADIN score reduces the complexity of the transcriptome into a tractable bivariate index that can be used to quantitate and monitor patients' disease status and progression. We deployed ALADIN in our studies of mouse AA, and demonstrated that ALADIN scores provide a robust quantitative measure of observed disease reversal, and "molecular distance to skin homeostasis" during the course of successful prevention and treatment of disease. ALADIN is currently being assessed in cross-sectional studies to validate its utility in human AA. We anticipate that ALADIN will be useful as a dynamic functional biomarker to stratify and longitudinally track patients enrolled in observational and interventional clinical studies.

1105

Differential effect of butorphanol on histamine itch, cowhage itch and heat pain sensitivity. A combined psychophysical and neuroimaging study

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Histamine and cowhage itches are transmitted via two distinct peripheral and spinothalamic neuronal pathways and project to the thalamus in subtly distinct nuclei. Furthermore, significant differences in the cortical processing of these two itch modalities have also been reported. Recent studies have implicated the PAR2-mediated cowhage itch pathway in pathological forms of chronic itch, and stressed the lack of therapeutic efficacy of antihistamines. From a molecular point of view, opioid receptors in the central nervous system are currently considered important relays for itch transmission. Butorphanol is a unique, mixed effect (μ-antagonist/κ-agonist) opioid that has analgesic and antipruritic actions. The aims of this study were first: to study comparatively the antipruritic efficacy of butorphanol on these two distinct pathways, when itch was induced experimentally using histamine or cowhage, as well as to assess the analgesic action of this opioid on heat pain (initially devised as a control for drug action). Secondly, we aimed to investigate drug's effect on cerebral perfusion and to dissect the basis of the antipruritic actions of butorphanol by functional MRI - Arterial Spin Labeling technique. Butorphanol completely suppressed the itch induced experimentally with histamine ($p<0.001$), while only reducing the intensity of cowhage itch by approximately 35% ($p<0.001$). More interestingly, butorphanol did not alter heat pain sensitivity, but only slightly affected the heat-pain associated unpleasantness (albeit non-significantly; $p=0.1$). Our neuroimaging data analyzed in 18 healthy and 11 atopic dermatitis subjects provides new insight into the underlying cerebral mechanisms, suggesting significant differences in the involvement of opioid receptors in the central processing of histamine vs. cowhage itch on one hand, and itch vs. heat pain, on the other.

1106

Incidence of invasion found during treatment of superficial/*in-situ* non-melanoma skin cancers by Mohs micrographic surgery

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Non-melanoma skin cancer (NSMC), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is the leading cancer worldwide. While treatment of invasive NMSC typically requires surgical excision, including Mohs micrographic surgery (Mohs), superficial and/or in-situ cases may be treated with topical agents, such as imiquimod and/or 5-fluorouracil. Given that a biopsy specimen is only a sampling of a lesion, while Mohs examines 100% of the margin, we sought to determine the incidence of invasion of biopsy-proven superficial/in situ NMSC following treatment with Mohs. We hypothesized that a significant portion of NMSC diagnosed as superficial/in-situ on biopsy actually harbor invasive disease on complete histological evaluation. This study also sought to identify predictive factors of invasion. A retrospective clinical study was performed across two Mohs surgery centers at UCLA, analyzing cases from January 1, 2012 - December 31, 2012, with initial biopsies evaluated by 5 different dermatopathologists, and surgically removed by 7 different Mohs surgeons. All cases identified as "superficial BCC," "SCC in-situ," or "Bowen's disease" that were treated with Mohs surgery were included. Operative notes and Mohs maps were reviewed for documentation of tumor invasion beyond the epidermis. Data regarding demographics and tumor characteristics was also collected and analyzed. Two-hundred thirty cases met the inclusion criteria for the study. Our results demonstrated that 58 of the 230 cases (25.2%) were invasive when reviewed during Mohs surgery (p-value < 0.01). Analysis of predictive risk factors (including age, sex, history of immunosuppressive medications, and/or tumor size) did not show statistical significance. In conclusion, our data provides evidence that a significant portion of biopsy-proven superficial/in-situ NMSC harbor invasion, and that treatment modalities that include a pathologic confirmation of tumor clearance should be strongly considered.

1107

Trans epidermal water loss measurement of skin surrounding venous leg ulcers

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The purpose of this study was to explore the applicability of Trans Epidermal Water Loss (TEWL) measurement technique to quantify different level of surrounding skin maceration in patients with venous leg ulcers. We prospectively examined 50 patients (39 females, 11 males) in the age range of 56-86 years old (mean age 69 _ 4 years) attending our wound clinic because of chronic venous leg ulcers. The patients clinical scoring for maceration was performed at an anterior and posterior surrounding skin site, midway between upper and lower margin of the ulcer by a blinded observer using a severity scoring system as follow: 0 = absent, 1 = minimal, 2 = moderate, 3 severe maceration. This scoring system is based on the degree of whiteness/redness and amount of area involved in surrounding skin to the ulcer involved. Measurements of Trans epidermal water loss (TEWL) were made at the same site assessed for clinical observation using a Vapometer_ (Delfin Technologies Ltd, Kuopio, Finland). For measurements, the Vapometer_ was used at standard room ambient conditions (25 °C, 55 % RH) and four consecutive readings were taken at the same site. The average value measured on the surrounding skin was significantly higher (167,16 g/hm2) than control side (46,8 g/hm2), ($p < 0.001$). Significant differences were seen when the TEWL values on surrounding skin and the clinical score of maceration were compared ($p < 0.001$). Clinical scoring was significantly correlated with different levels of TEWL. We evaluated 6 patients with maceration absent, 8 minimal, 26 moderate and 10 with severe maceration. Each group of patients showed, respectively, the following levels of TEWL: 89,07 g/hm2, 134,19 g/hm2, 166,98 g/hm2 and 274,5 g/hm2. Statistics showed an increase in TEWL values as the maceration clinical score increased ($r = 0.954$). Our results demonstrate the correlation between TEWL values and intensity of skin maceration, we can consider the TEWL as an objective parameter monitoring perilesional skin maceration.

1108

Delusions of parasitosis: A possible neuropathic component

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Delusions of parasitosis has traditionally been characterized as a psychiatric disorder manifesting with dermatological symptoms. Despite this, many patients do not improve on antipsychotic medications, and the pathogenesis of this condition remains unclear. Small fiber peripheral neuropathy can result from a variety of disease states, most notably diabetes. Damage to the small peripheral neurons of the skin can produce abnormal sensations such as paresthesias and dysesthesias. This underlying phenomenon is responsible for conditions such as post-herpetic neuralgia and erythromelalgia and can present with a spectrum of symptoms ranging from severe pain to pruritus. In this prospective study, we hypothesized that patients with delusions of parasitosis may have underlying neuronal abnormalities resulting in the symptoms associated with their disorder. Three patients diagnosed with delusions of parasitosis presented to dermatology with the complaint of infestation. To evaluate for the presence of neuropathy, a 3 millimeter punch biopsy was performed on each patient at a standard site on the distal leg. All three pathological specimens demonstrated abnormalities in dermal and epidermal innervation along with abnormal swellings within the neurites. The density of nerve endings was markedly reduced in each specimen. The final diagnoses were small-fiber polyneuropathy, early polyneuropathy, and a small-fiber axonopathy. While this exploratory assessment is limited by sample size, the presence of neuropathy in all three specimens suggests that there may be underlying neurological dysfunction contributing to the symptoms experienced by patients diagnosed with delusions of parasitosis. In addition, if a small fiber neuropathy is contributing to the sensation of infestation, medications such as gabapentin, pregabalin, and duloxetine may effectively improve symptoms and restore quality of life. This exploratory assessment suggests that delusions of parasitosis may be multifaceted in origin and further investigation studying the neurological abnormalities in this population is warranted.

1109

Sun-exposed forearm skin in African-Americans is not darker than sun-protected buttock skin, and pigmentation in both sites decreases with age

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Colorimeter can reliably assess skin pigmentation (L* value: 0=black, 100=white) and erythema (a*). Literature suggests that in Caucasians and Asians: 1) sun-exposed skin darkens with age; 2) sun-exposed skin (forearm) is darker than sun-protected skin (buttock); and 3) sun-exposed skin shows more erythema than sun-protected skin. Therefore, positive correlation exists between erythema and pigmentation in Caucasian and Asian skin. We investigated whether above associations hold true in African-Americans [AA]. Seventy-eight AA (20M, 58F; 18 to 91 year olds) were enrolled and colorimetry readings were obtained from buttock and dorsal forearm. Questionnaire exploring factors related to skin aging was also administered. In contrast to lighter skin types, AA skin showed decreased pigmentation with age (< 26 yo [N=10] vs. > 65 yo [N=8]) at both body sites, as indicated by higher L* values (buttock: 38.6±2.0 vs. 48.9±1.5 [$p<0.001$] and forearm: 41.8±1.8 vs. 47.9±1.4 [$p=0.018$]), respectively. Furthermore, in AA, sun-exposed forearm skin (42.9±0.6) was not darker than sun-protected buttock skin (41.4±0.7; N=78, $p=0.14$). However, similar to lighter skin types, erythema (a*) in AA was higher in forearm (12.0±0.1) compared to buttock skin (10.8±0.2, N=78, $p<0.001$). Therefore in AA, correlation between pigmentation (L*) and erythema (a*) was not seen in sun-exposed skin. Interestingly, in sun-protected skin of AA, L* and a * still demonstrated significant correlation ($r^2 = 0.35$, N=78, $p < 0.001$). No significant associations were observed between commonly reported factors that affect skin aging, such as sun exposure and tobacco use, and the colorimeter values in AA. Our data suggest that in AA, sun exposure may not be the primary factor that influences skin pigmentation in sun-exposed sites. Elucidating those factors that regulate AA skin pigmentation may lead to identification of novel targets and agents that may offer future treatments of pigmentary disorders.

1110

Identification of biofilm in acne vulgaris is an infrequent occurrence, seen more in non-inflammatory comedones than in inflammatory papules

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Acne vulgaris is a common multifactorial disorder of the pilosebaceous follicles. In recent years the role of *Propionibacterium acnes (P.acnes)* in triggering an inflammatory response has gained much attention. Although *P.acnes* is known to colonize pilosebaceous units in all acne prone individuals, development of acne lesions is not universal. We hypothesized that a trigger for inflammation in pilosebaceous follicles may reside in biofilm vs. the planktonic state of *P.acnes*. In this study we examined the presence of biofilm in non-inflammatory (comedones), inflammatory (papules), and uninvolved adjacent skin from acne patients. Fourteen patients with mild to moderate acne were enrolled (8 males, 6 females; mean age 28.6 years old [range: 18-40]). Skin specimens removed by punch instrument (3mm) were analyzed by confocal laser scanning microscope for the identification of biofilms (defined by large micro-colonies of > 100 cells) in the pilosebaceous unit. Of the 42 (14 x 3) skin specimens studied, 9 (21%) contained biofilm. Amongst acne lesions, biofilm was present in 8 (5 comedones and 3 papules) out of 28 (29%). In clinically normal skin, biofilm was observed in 1 sample. Our data indicate that biofilm is not present in the majority of acne lesions. Furthermore, it is present more frequently (almost 2-fold) in non-inflammatory comedones than in inflammatory papules. One speculation for this finding is that biofilm may be involved in the very early, rather than late stages of acne inflammation. Further elucidation of biofilm in acne will advance our understanding of its involvement in pathogenesis and the development of improved therapeutics.

1111

Low frequency Vancomycin-specific T cell responses are detectable in non-allergic individuals

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The association between specific HLA alleles and risk of severe cutaneous drug hypersensitivity reactions such as Toxic epidermal necrolysis is increasingly recognised. Vancomycin hypersensitivity reactions are not more common than for other antibiotics and no HLA association has yet been identified. To address whether individual predisposition is likely to be relevant in Vancomycin hypersensitivity reactions we set out to explore whether non-allergic individuals demonstrate circulating Vancomycin-specific T cell responses. We used ELISpot and [3H]-Thymidine assays to measure Vancomycin-specific ex-vivo IFN-γ / IL-4 and proliferation above background. 8 individuals with known drug hypersensitivity showed a mean circulating PBMC frequency of Vancomycin-specific cells of 87.0 $x10^{-4}$% (IFN-γ) / 32.5 $x10^{-4}$% (IL-4) and stimulation index (SI) 3.75, whilst individuals never previously exposed to Vancomycin (n=10) showed a lower mean circulating frequency: 5.47 $x10^{-4}$% (IFN-γ, p<0.01)) / 17.0 $x10^{-4}$% (IL-4, p=0.1) and SI 1.11. In controls who had been exposed to Vancomycin (without any evidence of a hypersensitivity reaction, n=4) detectable frequencies were also lower than allergics: 7.17 $x10^{-4}$% (IFN-γ) / 5.33 $x10^{-4}$% (IL-4) and SI 1.00. To confirm that low frequency responses were real, we co-cultured non-allergic PBMC with Vancomycin for two-weeks in vitro. We saw expansion of Vancomycin-specific T cells in ELISpot to an average frequency of 954 $x10^{-4}$% (IFN-γ) and 1130 $x10^{-4}$% (IL-4) which was confirmed by ELISpot and intracellular cytokine staining. Although Vancomycin-specific T cells were higher frequency in Vancomycin allergics, these data show that Vancomycin-specific T cells can be detected in non-allergic (non-exposed and exposed) individuals and that in vitro the cells can proliferate on encounter with the drug. Taken together, this suggests that both immune predisposition and potentially adaptive regulation may be important in development of hypersensitivity responses to Vancomycin.

1112

Grape seed antioxidants for preventing rosacea

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The purpose of the study is to explore the use of oral antioxidants derived from Chilean grape seeds in patients with rosacea in order to reduce or prevent symptoms of this disease. In Chile ultraviolet radiation is very high. This high ultraviolet radiation induces an increased production of antioxidants by the grapevine. The antioxidants were obtained and capsules of 500 mg were given to a group of 100 patients twice a day. An assessment of subjective symptoms, photographic comparisons and scanning of the skin were performed. A substantial reduction of more than 50% in redness and hot flushes was observed in patients taken oral Chilean grape seed antioxidants as compared with the same group of patients not taking oral antioxidants (p=0.05). These preliminary results may indicate that oral, and topical antioxidants derived from grape seeds from Chile may be used as a preventive measure for alleviating symptoms and discomfort that are very common in rosacea.

1113

Non-invasive measures of skin health and assessments of long-term efficacy of a sonic cleansing brush on skin of color

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A sonic cleansing brush was developed for daily facial cleansing. Long-term efficacy and safety of the sonic cleansing brush head was evaluated in two studies on skin of color (African American, Asian, Mexican-American, etc.). Methods: Safety/gentleness was evaluated in two studies [n=40 (study 1) and 66 (study 2), respectively] measuring Melanin (M), Skin Moisture/Hydration (H) & Erythema (E) at baseline, 4, 8, and 12 weeks of use. Duplicate measurements of M, H, E taken at each visit. Efficacy was evaluated in a 12 week, 4-visit home use study (n=66) using questionnaire data & before/after use photographs. Participants used the sonic brush for one minute with their normal cleanser whenever they cleansed their face (morning and/or bedtime). After cleansing participants applied skin care products they routinely used. Results: After 12 weeks of home use, 100% of subjects found the sonic brush more effective at cleansing then their previous method used. In addition, they perceived softer/smoother skin (100%), healthier appearing skin (96%), improved skin elasticity/firmness (84%), improved evenness of skin tone (78%), and brighter looking skin (90%). Parametric statistical methods were used to evaluate the safety/gentleness on skin of color. Dermaspectrometer measurements of Erythema and Melanin were consistent and remained unchanged throughout the studies, p=0.07(E). Hydration was significantly higher (p=0.011) at 12 weeks in study 1 but remained unchanged in study 2. Photographic results will be presented. Non-invasive measures of skin health confirm the gentleness of Clarisonic on skin of color with daily use; in additional product efficacy is supported though self-evaluations and photographic assessment.

1114

Evaluation of subsurface redness in individuals under long-term care for papulopustular and erythematotelangiectactic rosacea when adding a sonic skin care brush to their daily regimen

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Background: The National Rosacea Society (NRS) estimates that rosacea affects 1 in 10 women in the US and, in total, approximately 14 million people. Subtype 1 (erythematotelangiectatic) rosacea is associated with central facial edema and telangiectasias, most prevalent in Caucasian women (nearly 15 percent) compared to 1.5 percent with redness, papules and pustules indicative of subtype 2 (papulopustular) rosacea. Rosacea symptoms and severity fluctuate but may intensify with specific triggers (dietary, sun exposure, stress, etc.). Skin care and treatment of rosacea typically consists of gentle cleansing, topical and oral therapies [e.g. sodium sulfacetamide cleansers, prescription creams (e.g. metronidazole), and/or use of oral antibiotics], and limited sun exposure/use of sunscreens. While some mild symptoms of rosacea may persist, strict adherence to the prescribed skin care routine reduces the incidence of relapse or flare-ups; the NRS reports (in a multicenter study) that the rate of relapse was 42 percent in those not using medication compared to 23 percent of those who continued to apply a topical antibiotic. Methods: In this study, twenty-nine individuals under long-term care for rosacea were enrolled in a two-month study. Subsurface redness photos were captured using a VISIA camera. Image analysis (Image J software, NIH) was used to assess the intensity of redness of the center of the cheek at baseline and final visits. Results: Image analysis of subsurface redness is an effective means to assess erythema and the symptomatic state of individuals with rosacea. In the current study, the majority of individuals had a subsurface redness levels significantly decreased (p=0.036) over the course of the study (mean baseline redness value of 49.6; mean 2-month redness value of 43.7). Results provided indication that the sonic skin care brush may be routinely and favorably used for cleansing the skin of subjects with rosacea.

1115

Dermatology consultation may decrease telaprevir discontinuation among patients with severe triple therapy-associated rash

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Recently, telaprevir, a hepatitis C virus (HCV) serine protease, has been approved to treat chronic HCV in combination with pegylated interferon and ribavirin. This triple therapy has demonstrated efficacy, but its usage may be limited by adverse events, in particular rash. The hepatologists at an academic medical center enlisted the help of dermatology to evaluate and treat patients presenting with a severe (>50% total body surface area) triple therapy-associated rash with a hypothesis that early dermatologic intervention may increase treatment tolerability and decrease premature treatment discontinuation. Nine patients were referred to dermatology in 2011-12. Two patients were excluded because therapy was stopped prior to dermatologic evaluation. One woman and six men with a mean age of 61.9 years were included in analysis. Patients developed a rash a mean of 19.9 days after starting therapy and were treated with emollients, mid to high potency topical steroids and standing antihistamines. No patients had to stop triple therapy due to rash. Three patients had improvement of their rash but were taken off therapy for non-cutaneous side effects. Complete resolution of rash occurred between 6-151 days. Despite having a severe telaprevir rash, no patients had progression to a systemic drug reaction such as drug rash with eosinophilia and systemic symptoms or Stevens-Johnson syndrome/toxic epidermal necrolysis. Though limited by small sample size, this data suggests that early dermatologic intervention in patients with a severe triple therapy-associated rash may effectively decreases triple therapy discontinuation due to rash. Although, guidelines suggest telaprevir discontinuation in all patients presenting with a severe rash, this study demonstrates that patients may be able to safely complete therapy without rash progression. We therefore propose a reclassification of the telaprevir rash grading system to more accurately classify the severity of rash and to assist providers in effectively managing the bothersome symptoms of drug rash.

1116

Degos-like lesions in systemic lupus erythematosus treated with Rituximab

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Degos disease is a rare endovasculitis affecting small and medium-sized arteries, leading to tissue infarction. There are two variants, a cutaneous-only form with skin infarction, and a systemic form with infarction in the gastrointestinal tract or central nervous system. It has recently been suggested that degos lesions are actually a common end point of a variety of vascular insults, many of which have yet to be elucidated. Treatment is challenging and a standard therapeutic protocol does not exist. We present the case of a 19 year-old female with systemic lupus erythematous (SLE) and Raynaud's who presented with extensive degos-like skin lesions. Cutaneous examination revealed stellate porcelain-white macules and patches over the fingers, hands, and distal extremities, as well as loss of the digital pulp. Histopathology revealed low-grade vasculopathy with fibrinoid vascular change, intravascular fibrin, and extravasated red blood cells. Epidermal changes of LE were also identified. A visceral angiogram of the upper extremity revealed multifocal long segment arterial stenosis. A complete hypercoagulable work-up was within normal limits. The patient failed multiple therapies, including hydroxychloroquine, tapering doses of corticosteroids, mycophenolate mofetil, azathioprine, aspirin, enoxaparin, and pentoxifylline, before noting improvement on ritxumab. This case illustrates the rare presentation of degos-like lesions resulting from vasculopathy in the setting of SLE. Degos-like skin lesions have only rarely been reported in association with autoimmune diseases, allowing this case to augment the existing literature regarding this association. In addition, this is the first report, to our knowledge of degos-like lesions treated with rituximab. We therefore propose that rituximab be considered in cases of refractory degos-like lesions in the setting of SLE or other autoimmune diseases.

1117

Induction of procollagen I may not correlate well with clinical improvement in photoaging by retinoids

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We previously reported that the effectiveness of topical vitamin A (retinol=ROL) in improving photoaged skin can be comparable to tretinoin (retinoic acid=RA). This is consistent with prior bioassay data that ROL, a precursor to RA, results in similar retinoid skin pharmacology, albeit at higher concentrations. In some studies with RA, clinical improvement, primarily measured by wrinkle effacement, correlated with procollagen (procol)-I induction. Therefore, we hypothesized that molecular responses of photoaged skin to ROL and RA would be similar. Twenty-four subjects (2M, 22F; age range 40-84) with moderate to severe facial photodamage were treated for 24 weeks with 1.0% ROL or 0.02% RA once daily in a double-blinded manner. Improvement in the clinical severity score of 21% for ROL and 18% for RA was found to be comparable between the two groups. Biopsy samples were obtained at baseline (BL) and at week 24 (WK 24) and stained for procol-I. Blinded evaluator rated the slides for the degree (%) of dermoepidermal junction (DEJ) immunostaining. RT–PCR was used to assess procol-I gene expression. From BL to WK 24, no significant increase in procol-I DEJ immunostaining was observed with RA (BL=5%, WK 24=8%; N=11, p=0.18) and ROL (BL=8%, WK 24=11%; N=9, p=0.50) groups. Similarly, procol-I mRNA from BL to WK 24 did not change significantly in either group (RA=1.36x [N=5] and ROL=0.86x [N=5], p=0.12). Procol-I is a precursor molecule which requires enzymatic processing prior to being crossed-linked to collagen matrix. Furthermore, procol-I expression in human skin (mRNA and immunostaining intensity) can be reduced by acute UV irradiation. Therefore, procol-I has limitations as a reliable and durable measure of retinoid effects on photoaging. Quantifying an increase in cross-linked collagen may be a more accurate measure to correlate clinical improvement in photoaging with an agent of repair.

1118

Combination of topical nitrogen mustard and romidepsin demonstrates therapeutic synergy

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Combination therapy is standard in the treatment of Mycosis Fungoides (MF) and Sezary Syndrome. Nitrogen mustard (NM) is a topical alkylating agent, which has been successfully used in the treatment of cutaneous lymphomas since the 1950s with an overall response rate (ORR) of up to 83% in early stage MF. However, response rates are significantly lower in advanced stages. Romidepsin is a member of a new class of anti-cancer drugs known as histone deacetylase inhibitors (HDAC). Though its exact mechanism of action is still under investigation, romidepsin increases acetylation of histone proteins, resulting in increased gene transcription and pro-apoptotic proteins. Romidepsin is active in advanced CTCL, with the ORR of 34% and complete response (CR) of 6% in a cohort of 96 patients. We have successfully combined topical NM with romidepsin therapy in five patients who failed to achieve a significant partial response (PR) to romidepsin monotherapy. Three women and two men, with a mean age of 67 years, (range 52-83 years), stages IB, IIB and IVA (N=3), were treated with romidepsin at 14 mg/m2 for 1 to 4 months. Due to minimal response NM was added to the romidepsin regimen with responses noted on follow up within 1-2 months of NM use, with documented CRs (N=2) and significant PRs (near CR, N=3). At the time of this report, patients with CR are maintaining responses for 3 and 12 months. NM was applied to the entire body surface from neck down in erythrodermic patients, and to specific lesion in patients without erythroderma; frequency ranged from twice a week to daily, as tolerated. One patient discontinued NM one month after PR due to skin irritation. We hypothesized that this combination would result in improved clinical responses due to increased access of the alkylating agent to DNA during HDAC therapy and improved malignant cell killing. We have observed significant therapeutic synergy of these drugs in advanced staged CTCL without additional or unexpected toxicity in our case series. We conclude that further evaluation of this promising combination in a randomized clinical trial is warranted.

1119

Pemphigus erythematosus: A rare entity initially masquerading as toxic epidermal necrolysis

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Pemphigus erythematosus, a rare overlap syndrome with features of both lupus erythematosus (LE) and pemphigus foliaceus, is considered challenging to both diagnose and treat. We present the case of a 56-year-old female who was transferred to our institution and admitted to the burn unit for initial concern by an outside dermatologist for toxic epidermal necrolysis (TEN). Clinical examination revealed extensive erosions with scaling and crusting as well as scaly erythematous plaques, involving over eighty percent of the body surface area. Overall, the clinical presentation was that of an exfoliative erythroderma. Involvement was more pronounced over sun-exposed areas, including the face, scalp, upper chest, and back. Oral ulcerations and vaginal erosions were noted on examination, however, the palmoplantar surfaces were spared. Given clinical features inconsistent with TEN, a biopsy and laboratory work-up were performed. Labs were notable for an ANA of 1:2560, low C3 and C4, and positive anti-dsDNA, anti-Smith, anti-RNP, anti-Ro, and anti-La antibodies. Histopathology demonstrated acantholysis with dyskeratosis of the superficial epidermis. Direct immunofluorescence demonstrated intercellular IgG in the superficial epidermis, and mild discontinuous granular C3 deposition at the dermal-epidermal junction consistent with pemphigus foliaceous. This case illustrates an example of the rare clinicopathologic entity, pemphigus erythematosus, in which the target antigen is desmoglein 1, similar to as in pemphigus foliaceus. Even less common is the erythrodermic form of this disease, as presented here. Pemphigus erythematosus is frequently recalcitrant to therapy, often requiring immunosuppressive therapy. This patient was initiated on systemic corticosteroids, hydroxychloroquine, and strict photoprotection with improvement of her extensive cutaneous disease.

1120

Intralesional sodium thiosulfate for the treatment of cutaneous calciphylaxis

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Calciphylaxis is an often fatal vasculopathy frequently presenting cutaneously with retiform to stellate purpuric plaques that subsequently undergo necrosis and increase susceptibility to life-threatening infection. Intravenous sodium thiosulfate (STS) is an efficacious treatment for calciphylaxis; however, its usage may be somewhat limited in certain patients and institutions. In particular, intravenous STS is associated with adverse effects such as hypotension during rapid infusion, metabolic acidosis, volume overload, and gastrointestinal upset. Secondly, the cost, availability, and practicality of three times weekly dosing of intravenous STS may be restrictive factors. Therefore, developing an alternative approach to the treatment of calciphylaxis is desirable. Topical STS has been used effectively to treat calcium-mediated disorders. Additionally, in oncology, subcutaneous STS is currently the standard of care for the treatment of mechlorethamine extravasation injuries. We therefore hypothesized that intralesional STS may be an effective treatment approach to patients with calciphylaxis given the deep calcification observed in this disorder. In this retrospective case series, four patients with biopsy-proven cutaneous calciphylaxis were treated with intralesional STS (250 mg/ml) over weekly visits. Each patient tolerated the procedures well, only complaining of transient local pain during injection. Baseline and mid-treatment laboratories demonstrated no metabolic adverse events. Clinical photography was taken at each visit to monitor healing. All patients had decreased pain soon after initiating treatment and had remission of disease with complete wound healing within six months. Although this exploratory assessment is somewhat limited by the fact that some patients did not receive intralesional STS in isolation, it demonstrates that intralesional STS it a potentially safe and efficacious treatment for patients with calciphylaxis that warrants further study.

1121

Mechanic's hands are predictive of reduced lung diffusion capacity and interstitial lung disease in patients with dermatomyositis

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Previous studies suggest a high incidence of interstitial lung disease (ILD) in dermatomyositis (DM) with a considerable associated morbidity. We examined clinical predictors of interstitial lung disease in patients with DM. This is a chart analysis of a prospective cohort of patients with DM enrolled in the University of Pennsylvania Department of Dermatology CDASI (Cutaneous Dermatomyositis Disease Area and Severity Index) database. 105 patients were prospectively examined and the clinical data recorded since 2008. Mechanic's hands were defined by the presence of hyperkeratotic papules on the lateral surfaces of the fingers and on the palms. Patients with either an isolated reduced lung diffusion capacity or radiologically confirmed interstitial lung disease were analysed as an outcome group. 11 patients with missing data and 3 patients with juvenile onset dermatomyositis were excluded. 51 patients had classical dermatomyositis by Bohan and Peter's criteria and 40 patients had amyopathic or hypomyopathic dermatomyositis by Sontheimer's criteria. 84.6% of all patients were female, and 93.4% of all patients were Caucasians. The mean age at enrolment was 53.3 years and the mean age at onset of DM was 48.1 years. The mean duration of disease was 7.04 years and the mean duration of follow-up was 3.32 years. A statistically significant association was seen for the presence of mechanic's hands and the outcome analysed in patients with classical DM (odds ratio 3.90 (95% confidence interval =1.19-12.80), p=0.042), amyopathic DM and hypomyopathic DM (odds ratio 16.20 (95% confidence interval= 0.87-301.90), p=0.016) or all cases of DM (odds ratio 4.14 (95% confidence interval= 1.54-11.09), p=0.004). Mechanic's hands can be used as a surrogate clinical marker for an increased risk of having a reduced lung diffusion capacity or frank interstitial lung disease in patients with all subtypes of dermatomyositis.

1122

Effect of an elderberry extract rich in anthocyanins on skin ageing in postmenopausal women

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There is growing evidence that flavonoids may improve the skin's barrier function, increase thickness and elasticity and improve appearance and tactility (Heinrich et al 2006; Izumi et al 2007). In this placebo controlled parallel designed study, the effect on skin function and structure of oral administration of 500 mg/d of anthocyanins (as cyanidin glycosides; from elderberry) for 12 weeks, was assessed in 52 healthy postmenopausal women. At baseline and 12 weeks, the skin's transepidermal water losses (TEWL), hydration (corneometer), firmness and elasticity (torsional ballistometer), pigmentation (chromameter) and structure (phase-shift rapid In vivo measurement of skin from surface replica's taken adjacent to the eyes (PRIMOS)) were measured under controlled conditions. A skin biopsy was also taken for assessment of a range of matrix proteins. Following anthocyanin intake, skin was measured to be firmer (indentation at the temple; ANCOVA treatment effect -0.1mm, p=0.001), wrinkles were shallower and smoother (PRIMOS: Rt, ANCOVA treatment effect -62.8, p=0.03; Rz, ANCOVA treatment effect -21.3, p=0.01, Rmax, ANCOVA treatment effect -59.0, p=0.04) and skin pigmentation on the palm of the hand was darker (a* chrominance, ANCOVA treatment effect 1.1,,p=0.01; L* luminescence, ANCOVA treatment effect -1.5, p<0.001); the latter suggesting an increased blood flow at this site. The intervention, however, had no significant effect on skin hydration, TEWL or elasticity. In conclusion, these data suggest that consumption of 500 mg/d of elderberry anthocyanins may attenuate skin ageing in healthy postmenopausal women by diminishing age-related decline in skin firmness and development of wrinkles.